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THE EFFECT OF 17-ETHYL-19-NORTESTOSTERONE (NILEVAR) ON THE UPTAKE OF RADIOSULFUR IN THE FRACTURED HUMERUS IN THE RAT

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IT IS WELL KNOWN that any severe trauma, spontaneous or surgical, may result in an increase in the rate of protein breakdown in the body. This catabolic response to injury may be in part alleviated by an adequate intake of calories and protein. In clinical medicine, however, ancillary treatment with drugs promoting anabolism is frequently necessary.

Testosterone is the best known of the hormones possessing some regulatory effect on protein anabolism. Androgenic effects of this steroid make routine use rather difficult, and recently an attempt was made to find a substance promoting protein anabolism and yet devoid of masculinizing properties.

Between the synthetic analogues of androgenic steroids special attention was recently drawn on nilevar® (17-ethyl-19-nortestosterone). Saunders and Drill have shown that several nortestosterone derivatives exhibit relatively higher myotrophic potencies (anabolic effect) compared with androgenic effects as noted by response of levator ani muscle and seminal vesicles in the castrated rat.

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Definite anabolic effect of nilevar on human nitrogen metabolism following extensive abdominal surgery was reported by Peden and Maxwell. The clinical use of this substance was recently discussed by Drill and Saunders. These preliminary reports gave us an idea to investigate the effect of nilevar on the healing of fractured bone.

This problem presents great clinical importance. Various hormones influence the bone metabolism, and the best examples of this effect may be seen clinically in cases of certain hormonal deficiencies, which result in arrest of linear growth, osteoporosis, or spontaneous fractures.

In the present study the effect of nilevar on the healing of fracture was assayed by the radiosulfur uptake procedure. It was demonstrated previously by Dziewiatkowski (2, 3) that radiosulfur (S^{35}) shows a particular predilection for the cartilage when injected into animals. This isotope is selectively bound to certain elements of collagen and incorporated into the cartilage in organic form as chondroitin sulfuric acid.

It is known that sulfur amino acids labelled with S^{35} are taken up by the proteins of

TABLE I.—WEIGHT OF INTACT (W.I.) AND FRACTURED (W.F.) HUMERI OF RATS AND W.F./W.I. RATIO 3 WEEKS AFTER FRACTURE

Condition	*No. of rats*	*Values*	*Intact bone, mgm.*	*Fractured bone, mgm.*	*W.F./W.I.*
Normal control	20	Mean	272	330	1.21
		S.D.	±29	±35	±0.08
		Range	228–332	272–400	1.08–1.37
Castrated, no treatment	16	Mean	360	372	1.21
		S.D.	±57	±71	±0.13
		Range	262–485	240–511	0.96–1.51
Castrated, given 20 mgm. of nilevar	15	Mean	338	436	1.29
		S.D.	±33	±35	±0.11
		Range	307–400	391–505	1.11–1.59
Castrated, given 50 mgm. of nilevar	20	Mean	351	451	1.29
		S.D.	±27	±46	±0.16
		Range	320–400	405–610	1.05–1.90

TABLE II.—RADIOSULFUR IN INTACT (I) AND FRACTURED (F) HUMERI OF RATS AND F/I RATIO 3 WEEKS AFTER FRACTURE

Condition	*No. of rats*	*Values*	*Intact bone, c.p.m./100 mgm.*	*Fractured bone, c.p.m./100 mgm.*	*F/I ratio*
Normal control	20	Mean	354	776	2.24
		S.D.	±109	±183	±0.33
		Range	240–640	540–1140	1.72–2.92
Castrated, no treatment	16	Mean	323	392	1.04
		S.D.	±32	±45	±0.20
		Range	280–395	313–463	0.79–1.42
Castrated, given 20 mgm. of nilevar	15	Mean	321	1077	3.38
		S.D.	±96	±354	±0.50
		Range	180–590	590–2000	2.46–4.50
Castrated, given 50 mgm. of nilevar	20	Mean	266	1679	6.54
		S.D.	±45	±377	±1.85
		Range	184–311	1108–2405	3.58–9.58

regenerating wound tissue. It is also apparent that poor wound healing in animals with hypoproteinemia is associated with decreased accumulation of mucopolysaccharides and retarded collagen synthesis.

It seems evident from these data that the catabolic states disturb those processes of healing which may be well investigated by the radiosulfur. This isotope may be utilized for the study of the various stages of formation of collagen tissue during the process of healing and particularly for the study of normal and pathologic metabolism of cartilage and bone (4).

In our previous report (4) a method for the study of the uptake of radiosulfur in the bones of rats was proposed. We were able to demonstrate that the fractured humerus showed an increased uptake of S^{35} as compared with the uptake in the intact humerus of the same animal.

The purpose of our present study was to compare the uptake of radiosulfur of the fractured humerus with that of the symmetrically opposite intact bone in castrated rats which were treated or not with nilevar.

MATERIALS AND METHODS

Treatment. Adult male rats of the Wistar strain varying in weight from 212 to 280 grams and fed ad libitum with commercial Purina dog chow were used in the present study. Animals were castrated under ether anesthesia from 6 to 8 weeks preceding the fracture of the bones.

Under ether anesthesia a closed complete fracture of right humerus was produced in every rat by grasping the foreleg between fingers and thumb of each hand and snapping the bone at its midportion. The animals were kept in separate cages and all made a satisfactory recovery from anesthesia. Three weeks following the fracture they were sacrificed. Radiosulfur was given in dose of 200 microcuries by intraperitoneal injection 24 hours prior to sacrifice. The dose was dissolved in 2 milliliters of distilled water together with 8 milligrams of sodium sulfate.

Nilevar was administered by intramuscular injection, to two groups of castrated rats. The animals of the first group each received 10 injections of 2 milligrams of nilevar dissolved in 0.2 milliliter of sesame oil, the total dose per rat being 20 milligrams. The rats of the second series were treated by 10 doses of 5 milligrams of nilevar dissolved in 0.4 milliliter of sesame oil, the total dose per rat being 50 milligrams. The injections were given 3 to 4 times weekly during the 3 week period of healing of fracture. One group of castrated rats received no treatment and was used as a control. Another control group was constituted from normal noncastrated animals, submitted to fracture and S^{35} study.

Measurement of radiosulfur. After sacrifice of rats the fractured and normal humeri were removed, cleaned, and dried at room temperature for 24 hours, following which their weights were recorded.

The bones were then dissolved by the nitric-perchloric acid wet-digestion procedure described in detail in our previous report (4).

Final precipitate of radioactive barium sulfate was transferred to planchettes and the counting carried out by using a thin mica window Tracerlab G-M tube. A Tracerlab superscaler S.C. 18A was used for recording.

The results were expressed in counts per minute (c.p.m.) per 100 milligrams of tissue and F/I ratio was calculated. This is the ratio of the uptake (c.p.m./100 mgm. of bone) of S^{35} by the fractured humerus (F) to the uptake of S^{35} by the corresponding intact bone (I).

RESULTS

The results are summarized in Tables I and II and Figure 1.

Table I illustrates the difference in weight (W) between fractured (F) and intact bones (I) of rats in various experimental conditions. It may be seen that neither castration alone nor treatment with nilevar of castrated rats does effect the W.F/W.I ratio. This observation excludes the possibility that the findings concerning the S^{35} uptake might be related to the alteration of proportion of weight between intact and fractured bones.

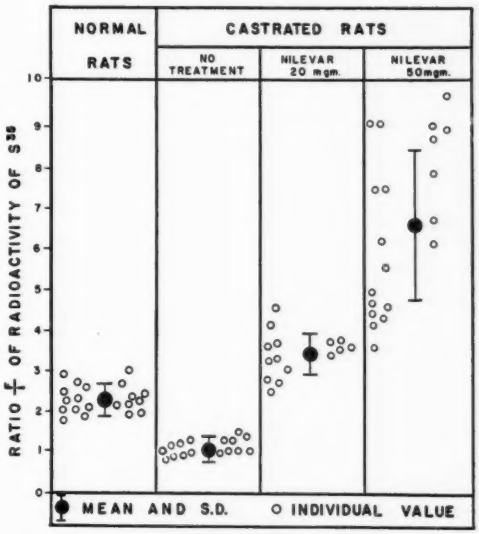

FIG. 1. Effect of nilevar (total dose 20 mgm. or 50 mgm. per rat) on S^{35} uptake by fractures (F) and intact (I) humerus, expressed as F/I ratio.

Table II gives a detailed account of the study of radioactivity of bones 3 weeks after fracture.

In accord with our previous data F/I ratios in normal control rats are about 2. There is significant reduction in this ratio in rats which were castrated prior to the fracture. But very significant increase of F/I ratio may be observed in castrated rats treated with nilevar, and it may be noted that the dosage plays an important role. This dose-response effect is better seen on Figure 1.

COMMENT

These results indicate that the proposed procedure of study of S^{35} uptake in healing fracture may be helpful in the evaluation of certain factors affecting the formation of callus.

The process of healing of fracture is apparently related to the synthesis of chondroitin sulfate in the newly formed collagen tissue.

It was shown that certain hormonal factors may influence the formation of cartilage by inhibition or stimulation of the synthesis of chondroitin sulfate. It results from the present experiment that such an inhibitory effect may be seen in rats after castration.

Nilevar not only restores to normal the ratio F/I but strongly stimulates the uptake of radiosulfur in healing fracture. This means apparently that nilevar has a marked effect on the synthesis of chondroitin sulfate in the collagen tissue as measured by the described S^{35} uptake technique.

SUMMARY

1. The study of the uptake of radioactive sulfur in the intact and fractured humeri of male rats was performed in normal and castrated rats treated or not with 17-ethyl-19-nortestosterone (nilevar).

2. The ratio (F/I) of radioactivity of fractured (F) to intact (I) bone was calculated.

3. Castration resulted in significant decrease of F/I ratio, as compared with normal control.

4. Nilevar given to castrated rats during the period of healing of fracture stimulated the S^{35} uptake in fractured bones resulting in F/I ratio which was several times higher than the same ratio observed in nontreated rats.

5. The response to nilevar was related to the dose in described experimental conditions.

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AN EXPERIMENTAL EVALUATION OF THE USEFULNESS OF ANTIBIOTIC AGENTS IN THE EARLY MANAGEMENT OF CONTAMINATED TRAUMATIC SOFT TISSUE WOUNDS

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THE EXPECTED INCIDENCE of infection developing in traumatic wounds following disaster is difficult to predict accurately because of the multiplicity of variable factors. Essentially, all traumatic wounds, when adequately studied, have been found to be contaminated with various species of bacteria. In an extensive study of wounds carried out from 1942 through 1943 by Meleney, the incidence of serious infection varied from 6.4 per cent to 21.8 per cent, depending in part on the type of wound.

During the Korean conflict at a time when the front was stable, Altemeier and Pulaski noted an incidence of significant infection in 26.5 per cent of 128 wounds which they examined.

The actual development of infection in any single wound is influenced by the presence or absence of a number of predisposing factors; for example: the time lag between wounding and definitive management; number, location, and extent of wounds; associated injuries; foreign bodies; type, number, and virulence of the contaminating bacteria; and the general condition of the patient.

Infection will undoubtedly be a major problem in the management of mass casualties inasmuch as the observed incidence of infection in traumatic wounds incurred under relatively ideal conditions is appreciable.

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Traumatic wounds, with their associated physiologic and anatomic derangements, including devitalized tissue, blood clots, and foreign bodies, are best treated by prompt and adequate surgical débridement. However, when confronted with the management of thousands of simultaneously incurred traumatic injuries, it would be impossible to carry out presently accepted standards of therapy. The temporary prophylactic use of antibiotic or chemotherapeutic agents in the management of large numbers of casualties is a possibility.

The usefulness of some of the chemotherapeutic and antibiotic agents in the prevention of infection in wounds has been studied in the past. The prophylactic use of oral sulfadiazine and the local application of a mixture of sulfadiazine and sulfanilamide to patients with soft tissue wounds, compound fractures, or burns did not decrease the incidence or severity of local infection or eliminate pathogenic organisms. However, the occurrence of generalized invasive infection was diminished in the treated group. Sulfonamides may also delay the appearance of infection by prolonging the so-called "Golden Period."

In a study by Cutler and associates, penicillin did not decrease the over-all incidence of infection in a group of patients with 250 soft tissue wounds and compound fractures; however, the penicillin dosage was much smaller than currently used. A number of

TABLE I.—CHARACTERISTICS OF MICROORGANISMS EMPLOYED

	Bacterial specie	*Cultural characteristics*	*In vitro susceptibility to antibiotics* Penicillin G	Oxytetracycline†
P-S, O-S*	Micrococcus pyogenes	Hemolytic, aureus, coagulase positive, phage type 44A	0.04	0.62
P-R, O-S	Micrococcus pyogenes	Hemolytic, aureus, coagulase positive	>50.0	6.2
P-R	Pseudomonas aeruginosa	—	>50.0	—
P-R, O-S	Escherichia coli	—	>50.0	3.1

*P=penicillin, O=oxytetracycline, S=sensitive, R=resistant.
†Minimum inhibiting concentration - mcgm./ml. except penicillin - units/ml.

investigators have shown that the development of gas gangrene was not prevented by small doses of penicillin. In experimental animals, larger doses of penicillin delayed the onset of gas gangrene. Among the newer antibiotics, chloramphenicol, chlortetracycline, and oxytetracycline have been found to be quite effective in the prevention and treatment of experimental gas gangrene.

In view of the foregoing, it is probable that antibiotics alone will not prevent local wound infection. There is some indication that the prophylactic administration of antibiotics may decrease the incidence of generalized invasive infection and prolong the period between the time of wounding and the development of localized infection. However, the over-all usefulness of antibiotics in the early management of contaminated traumatic wounds in the absence of adequate surgical débridement has not been defined.

The following experimental studies were designed to evaluate the usefulness of antibiotics in the early management of contaminated traumatic wounds in the absence of surgical débridement and to define broadly some general concepts which should be considered when choosing an antibiotic.

METHODS

Healthy rabbits of both sexes weighing 6 to 10 pounds were used. The animals were housed in individual cages for a 7 to 14 day period of acclimatization and then for a variable period of study. The cages were sterilized between experiments. Animals were allowed free access to water and a diet of antibiotic-free rabbit chow.

Experimental soft tissue wounds were produced which embodied the principal features of traumatic wounds: devitalized tissue, foreign bodies, and bacterial contaminants. The hair was shaved off the left buttock and thigh, and then the skin was well cleansed with an alcoholic soap solution. Operating room asepsis was employed. Under light ether anesthesia an area of skin measuring 3.5 by 3.5 centimeters and covering the left gluteus maximus muscle was excised. Three longitudinal incisions (each 3.5 cm.) were made through the entire thickness of the muscle; then three superficial vertical incisions (3.5 cm.) were made through the muscle sheath (Fig. 1). The inferior gluteal vein and branches of the inferior gluteal artery were severed. Each portion of incised gluteus maximus muscle, as well as the surrounding muscle, sciatic nerve, and skin, was crushed by using a Kocher clamp. No technique other than crushing was used to achieve hemostasis. Sterile dirt (0.5 to 0.75 gm.) was then mixed into the wound. Finally, the wound was inoculated with a suspension of bacteria in saline solution containing a known number of specific microorganisms of known susceptibility to antibiotics. The wounds were not dressed; however, the animals very seldom licked the wounds.

The general experimental aim was to compare the in vitro sensitivity of the contaminating bacteria with the effect of appropriate and inappropriate antibiotics on the progression of the experimental wound. In each experiment, antibiotic treated and untreated animals were compared. The animals to receive a given treatment in each group were determined before wounding by using a table of random numbers. Animals and data were coded until the completion of an experiment so that the observers were unaware of the specific treatment. All ex-

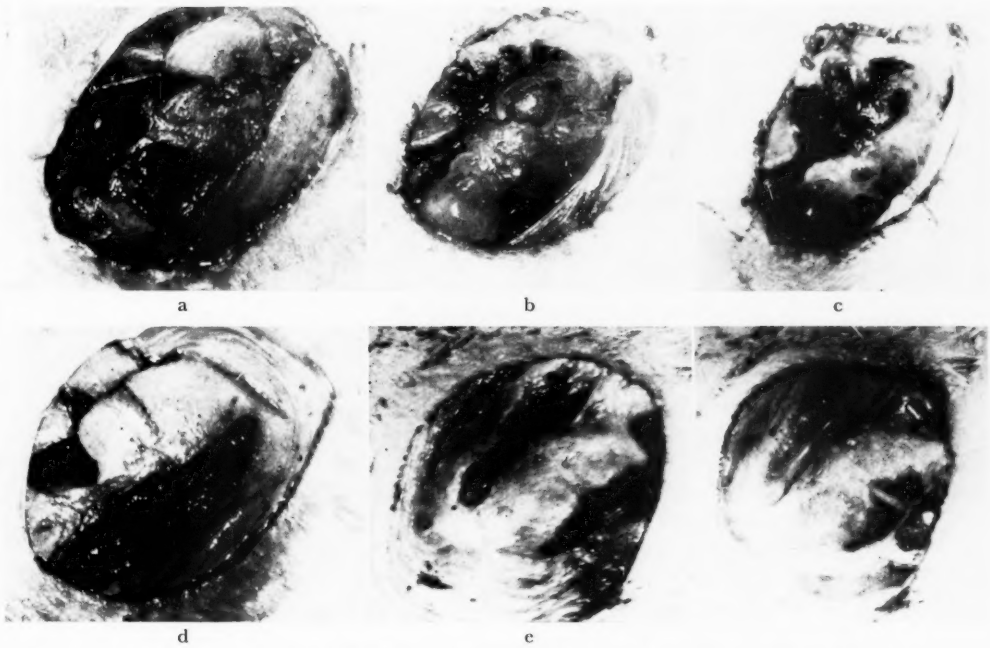

FIG. 1. A representative series of photographs taken of the wounds of a penicillin-treated and an untreated animal from one experiment. The wounds were primarily contaminated with a penicillin-sensitive Micrococcus pyogenes. a, b, c, Penicillin-treated; d, e, f, nontreated. a and d, 6 hours after wounding; b and e, 54 hours after wounding; c and f, 102 hours after wounding. Note that the penicillin-treated wound appears quite healthy at 54 hours, except for a small area of ischemia. By 102 hours, there is a small amount of purulent exudate in the wound. The untreated wound shows local suppuration by 54 hours, which has become marked by 102 hours.

perimental observations were repeated in at least 2 separate experiments.

The bacterial contaminants used were all isolated from human infections. Their characteristics are tabulated in Table I. Cultures were grown 18 hours at 37 degrees C. in trypticase soy broth, sedimented by centrifugation, and resuspended in saline solution (0.9 per cent) to concentrations ranging from 10^9 to 10^{10} bacteria per milliliter. Wounds were contaminated with 0.5 milliliter of the bacterial suspension. The number of bacteria in the inoculum was determined by the pour-plate technique at each experiment.

Several representative antibiotics, a bactericidal, and a bacteriostatic agent were used in these studies. Agents were chosen because of their specific action against the test organisms and not because they were necessarily superior in over-all activity to other antibiotic agents. All antibiotics were administered intramuscularly twice daily (8:00 a.m. and 5:00 p.m.) throughout the period of study. The dosages administered resulted in blood levels comparable in height and duration to those which might be attained in man with standard therapeutic regimens. The following regimens were used: (1) aqueous penicillin G, 1:1 mixture of potassium crystalline G, and aqueous procaine G, 3,000 to 20,000 units per pound administered twice daily; (2) chloramphenicol, intramuscular, suspended in 50 per cent solution of N, N dimethylacetamide, 12.5 milligrams per pound administered intramuscularly twice daily; and (3) oxytetracycline, suspended in saline solution, 2.0

milligrams per pound administered intramuscularly twice daily. Antibiotic administration was begun either immediately after wounding or delayed for 1½ or 6 hours.

Evaluation of the progression of the wounds was based upon the following: clinical observations twice daily, rectal temperature twice daily, leucocyte counts, blood cultures, wound cultures (quantitative and qualitative), and photographs 1 to 3 times weekly. Blood levels of antibiotics were found at the end of each experiment.

Clinical observations of the wound were recorded on coded cards. These included estimation of the degree of induration, erythema, muscle color and consistency, character and quantity of exudate, and wound odor. At the completion of an experiment, the cards were examined, and, on the basis of the observations, the time of onset of localized infection was determined.

Blood for culture and leucocyte counts was taken by cardiac puncture by using heparinized syringes. For culture, 1.0 milliliter of blood was incorporated into pour-plates by using trypticase soy agar so that the degree of bacteremia could be determined. Plates were incubated for 72 hours before discarding as sterile. Positive cultures were identified as to specific bacterial species, antibiotic sensitivity, and in some instances Micrococcus pyogenes were phage-typed to determine if they were of the same type as originally inoculated into the wound.

Both quantitative and qualitative cultures of the wounds were done. Swab cultures were taken by one person in a standard manner by swabbing around the circumference of the wound and then along each of the incisions in the muscle. Preliminary studies demonstrated that the quantity of material picked up by the swab was 110± 22 milligrams, depending upon the character of the exudate. The maximum variability seemed small enough to make the technique a useful parameter of comparison. The maximum variability in bacterial counts taken from the same wound with duplicate swabs was approximately 30 per cent. The percentage of bacteria estimated by the swab technique immediately following inoculation into a wound was within 50 per cent of the original inoculum. The swab was mixed in 9.0 milliliters of saline solution within a few minutes after swabbing the wound. The saline suspension was serially diluted and pour-plates made. Only plates containing 30 to 300 bacteria were counted. Aliquants of the original saline suspension were inoculated in trypticase soy broth and deep tubes of thioglycolate medium. Also, a drop of the original suspension was stained, and the relative percentages of gram-negative and gram-positive cocci and bacilli in approximately 200 fields were estimated. Aerobic cultures were picked to pure culture after 48 hours, while anaerobic cultures were incubated 7 days. Identification of the bacteria isolated from the aerobic and anaerobic broth cultures was based upon standard biochemical fermentation reactions. Members of the genus Clostridium were divided on the basis of motility and lecithinase production in 10 per cent egg yolk agar. Lecithinase positive, nonmotile bacteria were classified as Clostridium perfringens, while the remainder were classified as Clostridium species. Any Salmonella species isolated were typed using the Kaufman-White classification.

Blood levels of penicillin G were assayed employing the hemolytic streptococcus C-203 as the test organism and human type O blood as an indicator. The sensitivity of the test organism was 0.0156 unit per milliliter. Blood levels of chloramphenicol were measured in arithmetic dilutions of plasma using Bacillus cereus as the test organism. The sensitivity of Bacillus cereus was 2.0 micrograms per milliliter. Blood levels of oxytetracycline were measured in arithmetic dilutions of plasma using Staphylococcus aureus "SM" as the test organism. The sensitivity of staphylococcus "SM" to oxytetracycline is 0.2 microgram per milliliter. At each assay, a standard of the appropriate antibiotic was run in parallel with the plasma samples to be tested.

The duration of observation in the first group of experiments (39 animals) was 24 to 44 days. The subsequent experimental groups (295 animals) were followed closely for 6 to 7 days.

The effect of exposure of the rabbits immediately before wounding to sublethal quantities of total body x-irradiation on the progression of the wounds was studied in treated and nontreated animals. The experimental plan, treatment, and evaluation was similar to that employed in nonirradiated animals except that in each experiment x-irradiated and nonirradiated groups were studied simultaneously. Leucocyte counts, hematocrit determinations, and blood cultures were carried out daily or every other day. Wound cultures were not done. Animals received 400 roentgens in air total body x-irradiation while being rotated about a cephalocaudad axis. Irradiation factors were: target skin distance 60 centimeters, 36.4 to 42.0 roentgens per minute, filtration 1 millimeter of aluminum, 1 millimeter of copper, half value layer 2.1 millimeters of copper, 250 kilovolts, 30 milliamperes. In this strain of rabbits, by using these techniques, the minimal lethal dose (MLD) is approximately 800 roentgens.

The results between various groups and therapeutic regimens were subjected to statistical analysis by using four-fold contingency tables and the method of chi square. The Yates correction for continuity was used if any of the expected values were less than 10. Mean values were calculated and the standard error of the differences between means was compared by using the t test. Probability values of 0.05 or less were considered statistically significant.

RESULTS

The wounds in the first group of animals were contaminated with a strain of Micrococcus pyogenes var. aureus, P-S, O-S. The treated animals received 3,000 to 6,000 units of penicillin G (1:1 crystalline-procaine mixture) intramuscularly twice daily for the duration of the experiment. This group of animals was observed for a period of 24 to 44 days at which time healing of the wounds had occurred.

TABLE II.—IN VIVO EFFECTIVENESS OF PENICILLIN THERAPY IN RABBITS WITH NONDÉBRIDED WOUNDS PRIMARILY CONTAMINATED WITH PENICILLIN-SENSITIVE BACTERIA

	Nontreated		*Treated*		
Observations	*No./total*	*Per cent*	*No./total*	*Per cent*	*P*
Mortality*	7/15	47	3/24	12	<0.05
Bacteremia	8/15	53	5/24	21	>0.10
Leucocyte counts					
>15,000	3/15	20	1/24	4	>0.10
< 5,000	2/15	13	1/24	4	

Penicillin dosage: 3,000 to 6,000 units/lb. twice daily. Contaminant: M. pyogenes var. aureus.
*Mortality immediately following cardiac puncture excluded.

Contamination with a "penicillin-susceptible" microorganism followed very shortly by adequate penicillin treatment was specifically chosen in this first group of animals. If beneficial effects could not be demonstrated under these relatively "ideal" conditions, further studies would be of little value.

The mortality rate due to infection was decreased from 47 to 12 per cent in the penicillin-treated animals (statistically significant) (Table II). Death was considered to be the result of infection if associated with bacteremia, or if antecedent rectal temperatures were over 105 degrees F. and death did not immediately follow cardiac puncture. The maximum number of deaths in the untreated group occurred on the third day after wounding, while in the treated group all deaths occurred on the eleventh day.

Positive blood cultures were considered "significant" if 5 or more subsurface colonies per milliliter of blood were demonstrated on the pour-plates. The incidence of significant bacteremia was not significantly lower in the penicillin-treated group (Table II). The degree of bacteremia varied from a few bacterial colonies per milliliter to greater than 1,000 colonies per milliliter. The degree of bacteremia did not differ between the treated and nontreated groups, averaging 74 colonies per milliliter in treated and 102 colonies per milliliter in nontreated animals. The initial positive blood cultures occurred most frequently in the first week

TABLE III.—IN VIVO EFFECTIVENESS OF PENICILLIN THERAPY IN RABBITS WITH NONDÉBRIDED WOUNDS PRIMARILY CONTAMINATED WITH PENICILLIN-SENSITIVE BACTERIA

	Onset of localized infection, hours				
	Controls		*Treated*		
Delay in R_x hours	*No.*	*Mean ± SEM*	*No.*	*Mean ± SEM*	*P*
0	5	68 ± 10.0	5	112 ± 4.8	<0.01
1.5	5	40 ± 6.0	11	83 ± 4.4	<0.01
5	4	55 ± 12.4	6	79 ± 6.8	>0.05

in the untreated animals, and in the second week in the treated animals. All of the positive cultures except 1 contained only 1 bacterial specie. Seventy-seven per cent of the positive cultures were Micrococcus pyogenes var. aureus with the same antibiotic sensitivity as the original wound contaminant. Several of these Micrococcus pyogenes were phage-typed and were the same as the original contaminant. The bacteria isolated from the remaining positive blood cultures were Alcaligenes metalcaligenes. Alcaligenes metalcaligenes was isolated from 3 of the 5 penicillin-treated groups of animals developing bacteremia, and Micrococcus pyogenes was isolated from each of the 2 remaining animals. Micrococcus pyogenes was isolated from all 8 of the positive cultures in the control group.

The febrile responses in both groups were variable; however, rectal temperatures of greater than 106 degrees F. occurred more frequently in the control animals. Temperatures in the treated animals tended to return to baseline values of 103 degrees F. within 24 hours of wounding, while this return was delayed for an additional 24 to 48 hours in the control animals.

Leucocyte counts were quite variable in both groups; however, marked leucocytosis or leucopenia probably occurred more frequently in the nontreated animals (Table II). Weight changes were similar in the survivors of each group. There was an average weight loss of 6 ounces which persisted until the third week after wounding at which time both groups regained their prewounding weight.

One of the most striking observations was the delay in the onset of local wound suppuration as manifested by a persistence of apparently viable muscle, lack of local extension and a delay in the appearance of wound odor, erythema, induration, and purulent exudate. In animals treated immediately after wounding, this delay was about 60 hours (Table III). If the initial administration of 6,000 units per pound of penicillin was delayed until 6 hours after wounding, there was not a significant delay in the onset of localized infection. It should be emphasized that penicillin did not prevent the development of wound suppuration, but merely delayed the time of occurrence.

The quantitative bacterial counts per 100 milligrams of wound exudate are tabulated in Table IV. There were no differences in the total number of bacteria in the treated and nontreated wounds until approximately the thirteenth day, at which time the penicillin treated animals probably had greater total numbers of bacteria than did the control animals. Differential estimates of the percentage of gram-positive and gram-negative cocci and bacilli on a smear of wound exudate did not prove to be particularly valuable. In general, if gram-positive cocci such as Micrococcus pyogenes were inoculated into a wound, they tended to predominate (60 to 75 per cent of stained organisms) on wound smears for 24 to 48 hours. Gram-negative bacilli became predominant after

TABLE IV.—DIFFERENCES IN QUANTITATIVE BACTERIAL COUNTS

*Days post wounding**	*Nontreated*		*Treated*			
	No.	*Log bacterial counts ± SEM*	*No.*	*Log bacterial counts ± SEM*	*t*	*P†*
3	3	7.875 ± 0.120	6	6.909 ± 0.284	1.07	>0.10
		P = 0.05		‡P >0.50		
4	7	7.346 ± 0.198	9	6.688 ± 0.614	1.02	>0.10
		P >0.10		P >0.50		
7	3	7.685 ± 0.322	5	5.829 ± 1.260	1.42	>0.10
		P <0.01		P >0.50		
10	—	—	10	6.405 ± 0.220	—	—
				P >0.50		
13	4	5.248 ± 0.436	5	6.449 ± 0.338	2.31	=0.05
				P >0.10		
17	—	—	6	5.384 ± 0.435	—	—
				P <0.01		
23	—	—	5	3.241 ± 0.507	—	—

*Day of wounding counted as day 1, thus day 3 is 48 hrs.
†P values based on comparison of treated with nontreated animals at a given day after wounding.
‡P values based on comparison of consecutive days in either treated or nontreated groups.

the 24 to 48 hour period. No differences were detectable between the penicillin treated and control groups. The gram-negative bacteria in the wounds were probably the result of secondary contamination of open wounds.

The qualitative bacterial flora of these wounds was polymicrobic. An average of 6.2 bacterial species was isolated from each wound culture. The predominant bacterial species isolated were: Micrococcus pyogenes var. aureus and albus; Escherichia coli; Clostridium perfringens; nonhemolytic streptococci; nonspore-forming gram-positive aerobic bacilli; as well as coliform organisms. These consisted of Aerobacter species, Paracolobactrum species, Proteus species and Pseudomonas species. Penicillin treatment did not increase the percentage of Proteus or Pseudomonas species isolated.

The dose of penicillin G used to treat this group of animals was 3,000 or 6,000 units per pound of a 1:1 mixture of crystalline with aqueous procaine penicillin given twice daily. This quantity of penicillin gave excellent blood levels for 4 hours; however, by 8 hours there was no measurable circulating penicillin (Table V).

Granulation tissue became apparent during the third week after wounding, and healing occurred by about 30 days. The rate of closure and time required for complete healing was the same in the treated and nontreated groups.

On the basis of the observations of the apparent value of penicillin, particularly in delaying the onset of localized infection in nondébrided traumatic wounds contaminated with penicillin-sensitive Micrococcus pyogenes, further experimental groups were studied. These experiments were designed primarily to study the delay in onset of localized infection and to define broadly some of the factors which determined the usefulness of an antibiotic. The general plan was to contaminate wounds with bacteria of known antibiotic sensitivity in vitro, then to treat the animals with either appropriate or inappropriate antibiotics.

TABLE V.—ANTIBIOTIC BLOOD LEVELS

		*Blood level (u. or mcgm./ml.)**						
Antibiotic	*Dose*	*½ hour*	*1*	*2*	*4*	*6*	*8*	*16*
Penicillin	4,000 u.	9.4	7.3	5.2	1.6	0.08	<0.039	
	20,000 u.	19.4	20.0	13.3	9.2	3.1	0.8	<0.039
Oxytetracycline	2.0 mgm.	2.4	2.3	1.6	1.0	0.7		

*Mean levels based on 9 animals each. Penicillin levels in units/ml. Oxytetracycline levels in mcgm./ml.

These groups of animals were closely observed for a period of 6 to 7 days, at which time suppuration and infection had developed in most of the wounds, both treated and nontreated.

The dosage of penicillin used in these groups was increased to 20,000 units per pound of the 1:1 crystalline-procaine penicillin mixture given twice daily to provide longer periods of antibiotic coverage. Treatment was begun within 1 hour of wounding in all experiments. By using this therapeutic regimen, the animals had adequate blood levels for a minimum of 16 hours a day (Table V). Other groups of animals were treated with chloramphenicol or oxytetracycline. The observations on chloramphenicol treatment have not been included in the report because the absorption of chloramphenicol after intramuscular injection into rabbits was erratic and local sterile abscesses at the injection sites were frequently found. The blood levels of oxytetracycline attained are comparable to those which can be maintained in man on standard doses of oral oxytetracycline (Table V).

Five major experimental groups were studied. In the first group the effect of penicillin on the same strain of penicillin-sensitive Micrococcus pyogenes as used in preliminary studies was repeated; a comparison of the effectiveness of oxytetracycline and penicillin on this same strain of Micrococcus pyogenes makes up the second group (Table I). In the third group treatment with penicillin and oxytetracycline was compared in wounds contaminated with a penicillin-resistant strain of Micrococcus pyogenes. The effect of penicillin in wounds contaminated with Pseudomonas aeruginosa, which is highly resistant to penicillin, was studied

TABLE VI.—COMPARISON BETWEEN ANTIBIOTIC SENSITIVITY IN VITRO AND EFFECTIVENESS IN VIVO

Experimental group	*Bacterial contaminants* (antibiotic sensitivity)*	*Effect of antibiotics on onset of infection, hours*								
		Control			*Penicillin*			*Oxytetracycline*		
		No.†	*Mean ± SEM*	P^1‡	*No.*	*Mean ± SEM*	P^2	*No.*	*Mean ± SEM*	P^3
1	M. pyogenes (P-S)	26	43 ± 2.8	<0.01	27	118 ± 10				
2	M. pyogenes (P-S, O-S)	12	30 ± 3.1	<0.01	6	82 ± 8.5	=0.10	10	61 ± 8.2	<0.01
3	M. pyogenes (P-R, O-S)	22	33 ± 2.1	<0.01	21	42 ± 2.1	<0.01	8	77 ± 5.7	<0.01
4	Ps. aeruginosa (P-R)	14	52 ± 3.7	<0.05	15	66 ± 4.6				
5	M. pyogenes (P-S, O-S) and E. coli (P-R, O-S)	24	50 ± 3.1	<0.01	21	67 ± 2.9	=0.02	15	79 ± 4.1	<0.01

*P-S=abbreviation for penicillin-sensitive; P-R=penicillin-resistant; O-S=oxytetracycline-sensitive.
†No. of animals included in each therapeutic group.
‡P^1=comparison of means of control vs. penicillin; P^2=penicillin vs. oxytetracycline; P^3=control vs. oxytetracycline.

TABLE VII.—COMPARISON BETWEEN ANTIBIOTIC SENSITIVITY IN VITRO AND EFFECTIVENESS IN VIVO

Bacterial contaminants (antibiotic sensitivity)	*Effect of antibiotics*						
	Control			*Penicillin*		*Oxytetracycline*	
	No./total	*Per cent*	P^1†	*No./total*	*Per cent*	*No./total*	*Per cent*
I. Mortality							
1. M. pyogenes (P-S)*	1/26	4		0/27	0		
2. M. pyogenes (P-S, O-S)	1/12	8		0/6	0	0/10	0
3. M. pyogenes (P-R, O-S)	7/22	32	>0.20	3/23	13	0/8	0
4. Ps. aeruginosa (P-R)	0/15	0		0/14	0		
5. M. pyogenes (P-S, O-S) and E. coli (P-R, O-S)	0/24	0		1/21	5	1/15	7
II. Bacteremia							
1. M. pyogenes (P-S)	3/26	12		0/27	0		
2. M. pyogenes (P-S, O-S)	1/12	8		0/6	0	1/10	10
3. M. pyogenes (P-R, O-S)	1/22	5		0/23	0	0/8	0
4. Ps. aeruginosa (P-R)	2/15	13		1/14	7		
5. M. pyogenes (P-S, O-S) and E. coli (P-R, O-S)	0/24	0		0/21	0	0/15	0

*P-S—abbreviation for penicillin-sensitive; P-R—penicillin-resistant; O-S—oxytetracycline-sensitive.
†P^1—comparison of means of control vs. penicillin.

in the fourth group. In the fifth group the effects of either penicillin or oxytetracycline were compared in wounds contaminated with a mixed culture containing a penicillin-resistant, oxytetracycline-sensitive Escherichia coli and the same penicillin-sensitive, oxytetracycline-sensitive Micrococcus pyogenes as used in groups 1 and 2.

The comparisons between the in vitro antibiotic sensitivity of the contaminating bacteria and the effectiveness of various antibiotics on delaying the onset of localized wound infection are tabulated in Table VI. In groups 1 and 2, penicillin administration resulted in a mean delay in onset of infection of 75 to 52 hours (Fig. 1). Oxytetracycline was somewhat less effective than penicillin; however, the dosage of penicillin administered was relatively greater than that of oxytetracycline. Penicillin exerted a statistically significant though biologically minimal beneficial effect in wounds contaminated with penicillin-resistant bacteria (groups 3 and 4). Oxytetracycline was very effective in the animals with wounds contaminated with oxytetracycline-sensitive but penicillin-resistant Micrococcus pyogenes (group 3). In wounds contaminated with two bacterial species, one of which was penicillin-sensitive, while both were oxytetracycline-sensitive, penicillin was somewhat beneficial though oxytetracycline was superior. When the appropriate antibiotic was administered in these studies, the minimal mean delay in onset of localized wound infection was 29 hours. If an inappropriate antibiotic was administered, the maximal mean delay was 14 hours.

The mortality rate and incidence of bacteremia in these groups of animals were quite low in both the treated and untreated groups (Table VII). In general, the mortality rate was higher in the controls and in the groups treated with inappropriate antibiotics than in the animals treated with appropriate antibiotics. (Groups 1, 2, and 3:

TABLE VIII.—DIFFERENCES IN QUANTITATIVE BACTERIAL COUNTS

Bacterial Contaminants (antibiotic sensitivity)	Time post wounding, hrs.	Effect of antibiotics on bacterial counts: Control No.	Control Mean ± SEM	Control P^1†	Penicillin No.	Penicillin Mean ± SEM	Penicillin P^2	Oxytetracycline No.	Oxytetracycline Mean ± SEM	Oxytetracycline P^3
1. M. pyogenes (P-S)*	24	16	6.174 ± .297	<0.01	17	3.629 ± .471				
	72	14	7.254 ± .054	<0.01	15	4.693 ± .640				
	100	2	7.353 ± .100	>0.10	4	4.705 ± 1.694				
2. M. pyogenes (P-R)	24	7	7.611 ± .143	>0.10	8	7.429 ± .158				
	96	5	8.308 ± .141	>0.10	7	8.450 ± .142				
3. M. pyogenes (P-R, O-S)	18	8	7.685 ± .139	>0.50	6	7.796 ± .179	>0.10	8	7.601 ± .173	>0.50
4. Ps. aeruginosa (P-R)	72	14	7.910 ± .152	>0.10	15	8.261 ± .140				

*P-S=abbreviation for penicillin-sensitive; P-R=penicillin-resistant; O-S—oxytetracycline-sensitive.
†P^1=comparison of means of control vs. penicillin; P^2=penicillin vs. oxytetracycline; P^3=control vs. oxytetracycline.

TABLE IX.—EFFECT OF SUBLETHAL TOTAL BODY X-IRRADIATION ON IN VIVO EFFECTIVENESS OF ANTIBIOTICS*

	Controls: No x-ray No.	Controls: No x-ray	Controls: X-ray No.	Controls: X-ray	Penicillin: No x-ray No.	Penicillin: No x-ray	Penicillin: X-ray No.	Penicillin: X-ray	Oxytetracycline: No x-ray No.	Oxytetracycline: No x-ray	Oxytetracycline: X-ray No.	Oxytetracycline: X-ray
Onset of infection (Mean ± SEM hr.)	18	38 ± 3.0	17	32 ± 2.2	16	82 ± 7.6	13	88 ± 8	5	65 ± 16	5	57 ± 4.4
Mortality† (No./total)	—	1/18	—	5/17	—	0/16	—	1/13	—	0/5	—	0/5
Bacteremia (No./total)	—	2/18	—	2/17	—	0/16	—	0/13	—	0/5	—	1/5
WBC at 40 hrs. (1000's/mm.^{3})	11	9.63 ± 1.09	12	1.48 ± 0.41	9	10.49 ± 1.87	11	1.93 ± 0.40	5	10.36 ± 1.67	5	2.37 ± 0.58
Hematocrit at 96 hrs. (per cent)	6	30.9 ± 2.2	4	26.5 ± 2.9	5	30.7 ± 1.5	4	29.9 ± 2.1	—	—	—	—

*Animals received 400 roentgens total body x-irradiation. Wounds contaminated with M. pyogenes (P-S, O-S). Treatment begun within 30 minutes.
†Mortality rate within 10 days after wounding.

controls and inappropriate treatment, 12 of 83 died; appropriate treatment, 0 of 51 died $P<0.02$.)

The leucocyte counts and febrile responses were variable but in general corresponded to those observed in the first studies:

The effect of the larger doses of penicillin and oxytetracycline on the bacterial flora of the wounds was studied. The administration of penicillin to animals with wounds contaminated with penicillin-sensitive Micrococcus pyogenes kept the total bacterial counts per 100 milligrams of wound exudate suppressed significantly below control levels for 72 hours (Table VIII). The difference was not significant at 100 hours, which was slightly less than the mean time of onset of local infection in this group. In the control animals the bacterial population had almost reached maximal levels by 24 hours, even though the mean onset of clinical wound suppuration was 43 hours. Penicillin administered in inappropriate circumstances and oxytetracycline in relatively smaller doses had no effect on the total bacterial flora.

The qualitative bacterial flora was similar in all groups. Though penicillin was able to suppress the total bacterial population, Micrococcus pyogenes was eliminated from only 4 of 15 treated wounds, while disappearing from 1 of 14 nontreated wounds. All cultures yielded a polymicrobic flora similar to that observed in the earlier group.

The effect of sublethal total body x-irradiation on modifying the usefulness of appropriately chosen antibiotics was studied. Rabbits were exposed to 400 roentgens of total body x-irradiation 2 hours or less before wounding. The wounds were contaminated with the strain of penicillin-sensitive, oxytetracycline-sensitive Micrococcus pyogenes. Treatment was begun within 30 minutes after wounding. There were no significant differences in onset of infection, mortality rate, or incidence of bacteremia between x-irradiated and nonirradiated animals in any of the treated groups (Table IX). The effectiveness of either penicillin or oxytetracycline in delaying the onset of local wound suppuration was the same as ob-

served in the earlier studies (Table VI). The amount of exposure to x-irradiation, while sublethal, was sufficient to produce a marked leucopenia by 36 hours with return toward normal values by 96 hours (Table IX). The wounds in the x-irradiated animals were healed at approximately 30 days, which was the same as observed in nonirradiated animals.

DISCUSSION

Of all the measures designed to prevent infection in traumatic wounds, the most satisfactory prophylactic procedure is prompt, adequate surgical débridement. However, if confronted with the management of thousands of simultaneously incurred traumatic injuries, it would be impossible to carry out optimal surgical débridement. The temporary prophylactic use of antibiotic or chemotherapeutic agents as an adjunct to the early management of large numbers of casualties is a possibility.

Antibiotic prophylaxis should be divided into two types: complete prophylaxis and partial prophylaxis. In complete prophylaxis the administration of a suitable chemical or antibiotic compound suppresses, eradicates, or prevents a disease state; for example, the use of chloroquine in malaria. In partial prophylaxis suitable agents may modify the course of infection, but prevention, suppression, or eradication requires additional means; for example, infection in traumatic wounds. Antibiotics in this latter category are not and probably never will be primary therapy, though they may facilitate the handling of the basic problems which often require surgical correction.

In experimental, contaminated, nondébrided soft tissue wounds we again observed that antibiotics will not prevent the occurrence of localized wound infection. However, the occurrence of local extension and of generalized invasive infection as manifested by systemic toxicity, bacteremia, and death was decreased under certain experimental conditions. Likewise, the period between wounding and the development of localized wound infection was prolonged under the same experimental conditions. This delay in the development of infection seems to be adequate reason for the prophylactic administration of antibiotics to individuals with wounds in which there will be a delay in the primary surgical management of hours or even days.

The choice of a specific agent or agents is a controversial one. No one agent is entirely satisfactory, even for partial prophylaxis. The choice of the antibiotic for nonindividualized, wide-scale prophylaxis should be based in part on its antibacterial spectrum with regard to the microbial flora of traumatic wounds (clostridia, staphylococci, beta hemolytic streptococci, and coliforms), the ease of administration, the known side effects, and perhaps its mode of action. The early administration of large quantities of an antibiotic to experimental animals exerted little, if any, beneficial effect as regards decreasing the incidence of generalized infection or delaying the onset of localized wound suppuration if the wounds were contaminated with bacteria which were resistant to the antibiotic being administered. The slight effect noted with the large dosage of penicillin was probably its effect on secondary contaminants. Again, it should be emphasized that the choice of antibiotics used in these studies was based on their effectiveness against the specific test organisms employed and not because they are necessarily superior to other bactericidal or bacteriostatic antibiotics. Studies are currently in progress to ascertain the over-all in vitro susceptibility of the bacterial mixture found in street dirt from various locations, to evaluate the usefulness of various antibiotics in rabbits with wounds primarily contaminated with street dirt, and to compare further the in vitro and in vivo observations.

Rabbits exposed to amounts of x-irradiation which were sublethal but sufficient to induce a profound leucopenia responded in the same fashion as their nonirradiated controls. The failure of the irradiated animals to develop overwhelming bacteremia with

the contaminated wounds serving as the focus was somewhat surprising. However, overwhelming bacteremia does not seem to be an important feature in the syndrome of lethal total body x-irradiation in the rabbit as it does in the mouse, rat, and perhaps the dog. Oxytetracycline, which is bacteriostatic in action, was as effective in the x-irradiated animals as in the nonirradiated group. It was believed that a bacteriostatic agent might be less effective in the animal which was leucopenic and in which perhaps other antibacterial defense mechanisms were diminished as a result of the x-irradiation. If the amount of x-irradiation was increased to the midlethal range, these observations might not hold true. Yet the major clinical concern is with patients who might have received sublethal amounts of irradiation.

SUMMARY AND CONCLUSIONS

1. Experimental studies were carried out in rabbits to evaluate the usefulness of antibiotics in the early management of contaminated traumatic soft tissue wounds in the absence of surgical débridement.

2. The administration of antibiotics to these animals with nondébrided wounds did not prevent the development of localized wound infection. However, the period between wounding and the development of localized infection was prolonged under certain experimental conditions.

3. The early administration of either a bactericidal or a bacteriostatic antibiotic prolonged the period between wounding and the development of localized infection and decreased the incidence of systemic toxicity, bacteremia, and death, provided the wounds were primarily contaminated with bacteria which were sensitive in vitro to the specific antibiotic. The early administration of large quantities of an antibiotic exerted little, if any, beneficial effect if the wounds were primarily contaminated with bacteria which were resistant to the antibiotic being administered.

4. Exposure of rabbits to sublethal amounts of total body x-irradiation did not alter their response to these traumatic wounds or alter the effectiveness of either a bactericidal or bacteriostatic antibiotic if the wounds were primarily contaminated with bacteria sensitive to the particular antibiotic administered.

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PULMONARY VASCULAR CHANGES INDUCED BY EXPERIMENTALLY PRODUCED PULMONARY ARTERIAL HYPERTENSION

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THE PATHOGENESIS, life history, and reversibility of pulmonary vascular disease have acquired increasing significance because of the improved surgical treatment of congenital and acquired heart disease. The importance of pulmonary hypertension as an initiating factor in the production of pulmonary vascular disease has been pointed out previously (2). Marked pulmonary hypertension, which results in an acute arteritis leading to intimal proliferation and medial and adventitial hypertrophy, has been produced by anastomosing a left upper lobe pulmonary artery to the left subclavian artery. Vascular changes, consisting primarily of arterial medial hypertrophy, are not as marked when lesser degrees of pulmonary hypertension are produced. These studies, however, emphasized the end result of pulmonary hypertension rather than the pattern followed by reaching that end result. Although thrombo-embolization appeared an unlikely exciting agent in the production of pulmonary vascular changes, these studies did not conclusively establish their pathogenesis. The purpose of this report is to present evidence concerning the pattern of progression from the time the lung is subjected to a high intravascular pressure until the final vascular lesions have evolved.

METHODS

Pulmonary hypertension was created in the left upper lobes of mongrel dogs by the end-to-end anastomosis of the left subclavian and left upper lobe pulmonary artery. The anastomosis was made as large as possible. Control and follow-up pressures were obtained by inserting a needle connected to a Statham transducer at the following sites: left upper lobe pulmonary artery close to the lung parenchyma; in the subclavian artery (by passing the needle in a retrograde fashion through the anastomosis); the aorta; the main pulmonary artery; and, the left auricle. Control biopsies were sectioned from the left upper lobe and left lower lobe.

A left upper lobectomy was done from 1 to 11 weeks after the initial procedure. Pressures were again obtained. The gross appearance of the affected lung was noted and the size of the anastomosis recorded. The lung was then serially sectioned and elastic tissue and hematoxylin and eosin stains were made. A second left lower lobe control biopsy was also obtained.

RESULTS

Forty-one dogs comprised this series. Twelve animals died during the immediate postoperative period. Ten animals were found to have a thrombosed anastomosis. None of the animals developed cardiac failure. Left auricular pressures and main pulmonary artery pressures remained normal. Pressures obtained from the aorta and distal pulmonary artery during both operative procedures are recorded in Table I. In most instances, the distal left upper lobe pulmonary artery pressure approximated the aortic pressure and showed no significant change.

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TABLE I.—PRESSURE STUDIES, WEEK OF SECOND OPERATION

			Pressures, millimeters of mercury										
	Size of shunt, mm.		Subclavian		Left upper lobe pulmonary artery		Aorta		Main pulmonary artery		Left auricle	Per cent of mean pulmonary artery	Mean aortic pressure, per cent
Week	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	2nd		
1	4	4	92/67	87/57	87/67	80/75	97/78	77/57	24/13	23/11	—	90	111
2	2	2	95/80	92/75	95/80	95/80	102/86	100/85	21/13	22/12	4/0	93	95
3	2.5	2.5	58/43	90/65	55/40	85/57	55/40	91/62	17/15	15/6	5/0	100	94
4	6	6	95/75	80/57	95/75	72/57	110/95	77/57	22/9	20/6	7/0	85	94
5	5	5+	120/92	97/80	95/80	82/72	125/105	77/67	23/12	17/8	14/0	76	105
6	6.5	6.5	75/55	78/60	65/50	81/60	77/67	70/50	40/28	20/11	7/4	95	116
7	3.5	4.0	11/105	132/110	117/105	125/105	115/100	135/110	18/6	25/16	7/1	102	94
8	3	4	162/131	135/115	150/122	130/110	163/132	147/120	43/22	28/13	6/1	92	89
10	4	3.5	102/84	100/72	100/85	82/75	82/67	96/57	—	26/16	8/1	123	94
11	5	4	78/62	117/105	65/58	124/102	70/65	116/102	—	26/14	—	90	103

The progression of changes in the pulmonary vascular bed followed a distinctive pattern. The control biopsy taken from the left lower lobe appeared normal in every respect. The alveoli were opened and found to be thin-walled. The pulmonary arteries were likewise found to be thin-walled and wide-lumened, and the capillary bed was normal. The left upper lobe control tissue taken immediately after opening the anastomosis showed the presence of definite pathologic changes. The vascular bed appeared engorged and dilated, and areas of intra-alveolar hemorrhage were seen.

Changes near the anastomosis had progressed over a period of 1 week. There was marked dilatation, engorgement, and tortuosity of the entire vascular tree. Widespread parenchymal hemorrhage was present, and areas of hemorrhage were noted in and around the small muscular pulmonary arteries. The outermost elastic fibers of the elastica externa were frequently separated from the remaining media by a layer of red cells. The elastica interna frequently appeared fragmented. There was actual wall disruption and necrosis of some small muscular arteries. The subintimal and medial layers of some vessels were infiltrated by polymorphonuclear leucocytes and round cells, producing a partial obstruction. The invasion of the media by leucocytes distinguished these lesions from acute thrombus formation. In other vessels, a cuff of leucocytes, round cells, and red blood cells was found surrounding the vessel and often invading the adventitia.

Sections obtained 3 weeks after the initial operation revealed a decrease in the amount of intra-alveolar hemorrhage and edema and decreased alveolar wall thickening. There were areas of focal atelectasis, bronchitis, and pneumonitis. The red blood cells previously seen in the adventitia and perivascular spaces of the small muscular pulmonary arteries were partially replaced by round cells and by an acid-staining collagen material. Lumen-wall ratio studies of the small muscular pulmonary arteries revealed a decrease in ratio, indicating a relative increase in medial hypertrophy (1).

At 6 weeks, gross evidence of medial hypertrophy was present accompanied by a further increase in perivascular collagen. Fragmentation of the elastica interna was marked. At 8 weeks, practically all arteries were involved. Alveolar wall thickening had almost disappeared. Heavily pigmented macrophages were seen within the alveoli.

A complete picture of pulmonary vascular disease evolved 11 weeks after the first operation. Sections at this time were characterized by tremendously thickened vessels surrounded by avascular thin-walled alveoli with a total decrease in visible capillaries. Many arteries were thickened by a decided increase in adventitial collagen; excessive medial hypertrophy and intimal proliferation were sufficient in some to cause complete obstruction of the lumen. The intimal proliferation appeared fibrous and acellular. In other vessels, the microscopic anatomy of the vessel was partially or totally destroyed. The artery appeared as a cellular granulomatous lesion.

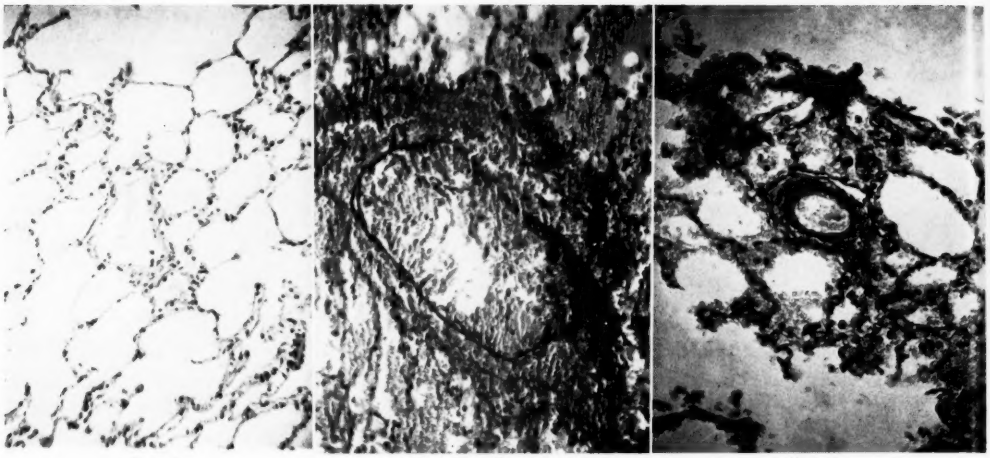

FIG. 1. FIG. 2. FIG. 3.

FIG. 1. Control biopsy, left lower lobe. Note the thin-walled muscular pulmonary artery and the normal appearance of the alveolar walls.

FIG. 2. One week biopsy. Left upper lobe. Note the perivascular hemorrhage with invasion of the adventitia and a point of rupture of the vessel wall. Note the alveolar hemorrhage and swelling of the alveolar walls.

FIG. 3. Six weeks' biopsy, obtained from periphery of the left upper lobe. Note the slight medial hypertrophy, thickening of the alveolar walls, and presence of macrophages in the lung parenchyma.

The media appeared thin and fibrosed, and the intima was cellular. Endothelium-lined spaces, found chiefly in the perivascular zone, were present in all layers of the artery. Serial sections of these lesions indicated that they involved the small muscular arteries at the point of bifurcation from a larger pulmonary artery. The endothelium-lined spaces communicated with the arterioles.

Changes in the peripheral areas of the left upper lobe were not as rapid. At 3 to 5 weeks, the periphery contained changes comparable to those seen at 1 week close to the anastomosis. Thus, there appeared to be a gradual spread from the site of the anastomosis out toward the periphery. Within 11 weeks, however, the changes were relatively uniform throughout the lobe.

DISCUSSION

The response of a lung to the sudden fivefold increase in intravascular pressure follows a characteristic pattern. The initial reaction is dilatation and engorgement of all available vascular pathways. Evidence of vascular and parenchymal injury then appear. Injury to the vessel wall is indicated by: (1) the presence of perivascular and intra-adventitial hemorrhage; (2) fragmentation of the elastica interna and externa; (3) actual rupture and necrosis of the vessel wall; and (4) an isolated or diffuse inflammatory response. Injury to the parenchyma is indicated by: (1) alveolar hemorrhage and edema; (2) interstitial edema; and (3) the later appearance of macrophages within the alveoli. The sequence of changes noted in the small pulmonary arteries probably results from stress. The high pulmonary artery pressure causes dilatation and stretching to the extreme limit. Overstretched muscle becomes necrotic. Plasma and red blood cells seep into the vessel wall and elicit an inflammatory response. The degree of vessel destruction and the severity of the inflammatory process are probably directly related to the type of vascular lesion produced. Red blood cells and plasma within the wall of the vessel are replaced by round cells and then by collagen material. There is a

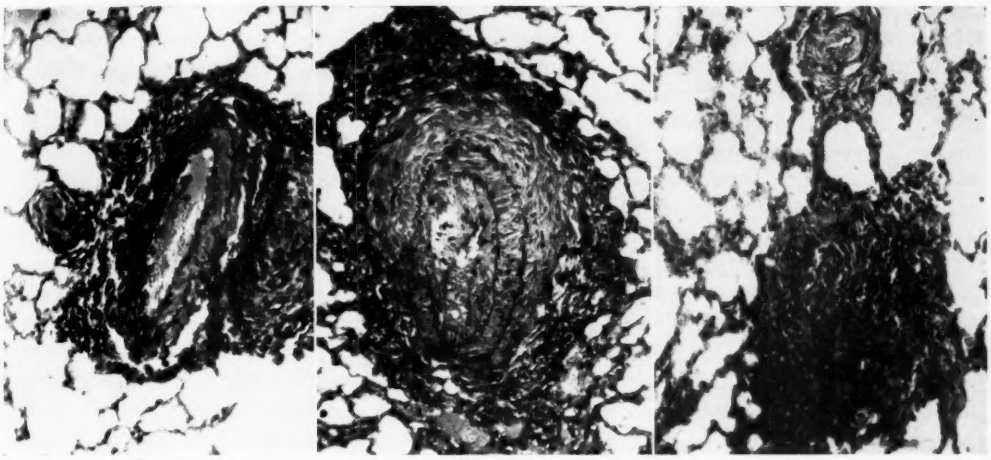

FIG. 4. FIG. 5. FIG. 6.

FIG. 4. Six weeks' biopsy, obtained close to the anastomosis. Note the markedly thickened small muscular artery and the 2 obliterated arterioles. Note the thin alveolar walls.

FIG. 5. Eleven weeks' biopsy. Left upper lobe. Note the extreme thickening of all areas of the vessel and the perivascular inflammatory response.

FIG. 6. Eleven weeks' biopsy. Left upper lobe. Note the loss of anatomy, the cellular proliferation, and the endothelium-lined spaces.

total increase in fibrous tissue of the adventitia and all components of the media. Injury results in an intimal proliferation. This may be acellular or characterized by a markedly cellular appearance combined with the occurrence of multiple endothelium-lined spaces, both within the media and throughout the vessel wall. This latter lesion probably represents a more severe or acute injury pattern in which the injury is actual disruption of the arterial wall followed by invasion of the entire wall with leucocytes and a subintimal heaping of inflammatory cells. In such vessels medial hypertrophy is less marked than when the intimal proliferation appears acellular.

Clearing occurs in the lung parenchyma as vascular narrowing progresses. Alveolar and interstitial hemorrhage and edema disappear, capillary dilatation subsides, and normal appearance of the alveolar wall returns. The difference in response of the lung parenchyma and arterial wall is probably related to the length of time the stressing force acts upon each. A high intra-arterial pressure continues, but strain on the lung parenchyma ceases after vessel changes are completed, for an effective barrier has been built between the high pressure in the pulmonary artery and the distal capillary bed.

The explanation for the gradual spread of changes toward the periphery is more difficult. Hemorrhage and edema involving the vessels and adjacent areas are the immediate effect of the high pressure. Because of this hemorrhage, extravascular pressure is significantly increased and consequently the effective intravascular pressure is reduced. Distal to the area of injury, vessels are protected by the increased extravascular pressure in the area of injury, and findings consist only of vascular engorgement and dilatation. As healing takes place, extravascular pressure is reduced. Effective intravascular pressure consequently increases and sufficient pressure is transmitted toward the periphery to cause new areas of edema and hemorrhage. Only after a period of time do vessel wall changes become sufficient to produce an effective obstruction to blood flow.

The fully developed vascular lesions seen throughout the lung within 11 weeks follow-

ing the creation of pulmonary hypertension cannot be differentiated from the end result of thrombo-embolization. However, examination of sections taken at weekly intervals did not reveal the presence of thrombi. Vessels in which leucocytic invasion of the medial and subintimal layers causes luminal obstruction might be considered as having infected thrombi. However, the precursor of such lesions appeared to be a rupture and necrosis of the vessel wall. Such lesions were relatively infrequent. Hypertrophy of all layers followed by sufficient intimal fibrosis to occlude the vessel was far more common.

SUMMARY AND CONCLUSIONS

An anastomosis between the distal left upper lobe pulmonary artery and left subclavian artery produces severe pulmonary hypertension in the left upper lobe.

Weekly studies following an anastomosis reveal a progressive vascular pattern which appears to be a direct result of vascular injury.

The sequence of change is as follows: (1) marked dilatation, engorgement, and tortuosity of the entire vascular tree; (2) disruption of intima, fragmentation of elastic fibers of the elastica interna, and occasional necrosis of vessel wall; (3) hemorrhage into the arterial wall, perivascular space, and alveoli; (4) inflammatory reaction characterized by invasion of the vessel wall, or (5) deposition of fibrous material in the adventitia and intima and hypertrophy of the media; (6) partial or complete occlusion of the small pulmonary arteries due to intimal fibrosis or a cellular intimal proliferation containing numerous endothelial lined spaces; (7) a clearing of parenchymal hemorrhage and interstitial edema as the arterial lesions progress.

These changes appear to spread concentrically from the shunt toward the periphery of the lung.

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FUNCTIONING AND NONFUNCTIONING ADRENAL CORTICAL TUMORS

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PRIMARY TUMORS of the adrenal cortex are comparatively rare. In the medical literature they are most frequently reported as single cases. Because of their infrequent occurrence some features of their clinical behavior and pathologic anatomy are not widely known. For this reason the recording of the 16 cases from the Surgical Pathology Laboratory of Washington University School of Medicine is thought to be worth while. These include 6 cases from the St. Louis Children's Hospital, 7 cases from Barnes Hospital, and 3 outside cases, the tumors and clinical histories of which were sent to the laboratory for consultation. Rapaport and associates reviewed a 20 year experience with adrenal tumors, including the years 1930 through 1949. We have reviewed cases reported in the available literature including 1950 to 1955, and have summarized some features of these cases.[1]

CLINICAL FEATURES

There is, of course, no constant clinical syndrome associated with adrenal cortical tumors. The symptoms and signs depend on the type of cortical hormones elaborated by the tumor, as for example, the virilizing syndromes are associated with excess production of androgens, and Cushing's syndrome with the excess production of hydrocortisone-like substances.

Less commonly, other types of cortical hormones may be secreted and produce distinctive derangements. Estrogen-secreting tumors may produce feminization, chiefly gynecomastia in males or sexual precocity in female children. Excess aldosterone production results in hypertension, muscle weakness, sodium retention, hypokalemia, and alkalosis. We have seen no examples of pure estrogen-producing or aldosterone-producing tumors. Mixed syndromes, which may be attributed to the effects of more than one class of hormones, are frequent. In the present series, there are cases which are chiefly virilizing but which exhibit also some features of Cushing's syndrome, and vice versa. These are classed according to the predominant clinical effect. We found that adrenal tumors are less apt to produce a "pure" syndrome than the adrenal hyperplasias are.

There are 3 nonfunctioning carcinomas of the adrenal in the present series. One of these patients presented with right upper quadrant pain, another with a large retroperitoneal mass, and the third with the appearance of metastases, illustrating the 3 chief symptoms by which the nonhormonal tumors make themselves known. Huge masses may develop and cachexia is common.

Virilization may occur as sexual precocity in a male child (Case 12) or as masculinization of a female, either child (Case 5, Fig. 1) or adult (Case 2). Excess androgen production is quite rare in the adult male. Commonly, in the adrenogenital syndrome, there is hirsutism of male distribution, acne, deepening of the voice, hypertrophy of the clitoris, and amenorrhea in the adult female. Muscle development may be prominent (infant Hercules). Rise in blood pressure and mental aberrations do not usually occur.

In our cases virilization occurred as the sole or predominant pattern in 6 cases. One of these cases was in a male, and 5 were in

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[1]The bibliography does not include all of the reports reviewed in the interest of conservation of space. The 83 cases reviewed were reported in 49 articles.

FIG. 1. Pubic hair of a 1½ year old girl with a benign adrenal tumor.

females. As seen in Table I, about 83 per cent of cases of virilization due to adrenal tumor occur in females. Half occur before the age of 12 and half later in life.

The chief symptoms and findings in Cushing's syndrome are central obesity with acral wasting, mental changes chiefly profound depression, florid round face, bruising, purplish striae, hypertension, amenorrhea, susceptibility to infections, poor healing of wounds, and back pain, occasionally with collapse of vertebrae. Facial and body hair may appear but scalp hair is coarse and thinned-out. In our cases, the pure syndrome occurred 4 times. The 3 other cases classed as Cushing's exhibited some androgenic features. Table I shows that 80 per cent of the adrenal tumors producing Cushing's syndrome occur in women, which is similar to the sex distribution of the androgenic tumors. However, a larger percentage (76 per cent) of the cases of Cushing's syndrome occur in persons over 12 years of age.

RADIOGRAPHY

Since the signs and symptoms of hypercorticism due to tumor may differ in nowise from those due to adrenal cortical hyperplasia, the diagnosis of tumor is usually made at operation or by x-ray study. In only 3 of our cases of functioning tumor was the tumor palpable. Plain films of the abdomen and intravenous pyelography may give evidence of tumor, as they did in 10 out of 13 of our cases. Presacral oxygen insufflation may give better detail, but in no case in our experience did it outline a tumor which had not been seen in the plain films. On several other occasions, tumor was diagnosed by oxygen insufflation, but no tumor was present at operation. We do not employ presacral insufflation as a routine part of the study of patients with hypercorticism. Calcification may occur and usually indicates that the tumor is malignant (Fig. 2). Pyelography may demonstrate that the kidney on the involved side is depressed and the upper pole tilted anteriorly and laterally (Fig. 3a and b).

In children, virilization may result in advanced bone age (Case 14), whereas

TABLE I.—CLINICAL DATA

		Females				*Operative mortality*	
	No.	*No.*	*Per cent*	*< 12 yrs.*	*> 12 yrs.*	*No.*	*Per cent*
	CUSHING'S SYNDROME						
Collected cases (Rapaport *et al.*) 1930–1949	117	97	83.0	26	90	40/71	56.3
Collected cases 1950–1955	48	22	68.7	8	24	7/34	20.6
Authors' cases	7	4	80.0	4	3	4/7	57.1
Totals	172	123	80.0	38 (24%)	117 (76%)	51/112	45.5
	ADRENOGENITAL SYNDROME						
Collected cases (Rapaport *et al.*) 1930–1949	72	63	87.5	40	32	15/52	29.0
Collected cases 1950–1955	35	26	74.3	16	19	2/35	5.7
Authors' cases	6	5	83.0	2	4	0/6	0.0
Totals	113	94	83.2	58 (51%)	55 (49%)	17/93	18.3

Cushing's syndrome may be associated with retarded bone age (Case 15).

LABORATORY

Characteristically, the virilizing syndromes do not exhibit abnormalities in the blood counts, carbohydrate metabolism, or plasma electrolytes. The diagnosis is confirmed by finding increased amounts of 17-ketosteroids in the urine, which may occur in virilizing syndromes due to either tumor or hyperplasia of the adrenal cortex, although the amount excreted is generally higher in the tumor cases. Allen's test for dehydroisoandrosterone may be useful in differentiating tumor from hyperplasia, since those patients excreting very large amounts of dehydroisoandrosterone were all found to have tumors.

In Cushing's syndrome polycythemia is encountered frequently. It was present in all of our cases of Cushing's and mixed syndrome. There may be a leucocytosis with a lymphopenia and a decrease in circulating eosinophiles. The glucose tolerance curve often is diabetic in type with increased insulin resistance. There is increased capillary fragility. Osteoporosis is very frequent. Hypokalemic hypochloremic alkalosis has been observed in Cushing's syndrome, but none of our patients exhibited abnormalities in the plasma electrolyte concentrations. Sodium retention may occur, however, and be associated with an expanded extracellular fluid volume rather than elevated plasma sodium levels. The patient in Case 3 showed a large diuresis of sodium in the first few days after removal of the tumor. On the third postoperative day, while receiving 0.16 mol of sodium intravenously (no oral intake), she excreted 0.40 mol of sodium in the urine. Ordinarily, after a nonendocrine operation of this magnitude, one would expect a positive sodium balance.

The urinary excretion of both 17-ketosteroid and 17-hydroxycorticosteroid are apt to be higher in Cushing's syndrome due to malignant tumor than in Cushing's syndrome with adrenal hyperplasia. The extremely high values are found chiefly associated with adrenal carcinomas.

FIG. 2. Calcification in a left adrenal carcinoma. The calcified tumors are usually malignant.

The administration of cortisone will suppress urinary excretion of 17-ketosteroids in cases of Cushing's syndrome or virilization due to adrenal hyperplasia but does not usually affect urinary excretion of 17-ketosteroids in cases due to tumor. This was true in the only one of our cases so studied (Case 3). Before giving cortisone, the daily 17-ketosteroid excretion ranged from 33.9 to 37.3 milligrams and immediately afterward ranged from 49.7 to 55.5 milligrams. ACTH given to this patient resulted in a slight elevation in 17-ketosteroid excretion, from 59 to 61 milligrams to 68 to 74 milligrams per day.

Laboratory results in our cases are shown in Table II. In the 6 cases in which both 17-ketosteroid and 17-hydroxycorticosteroid

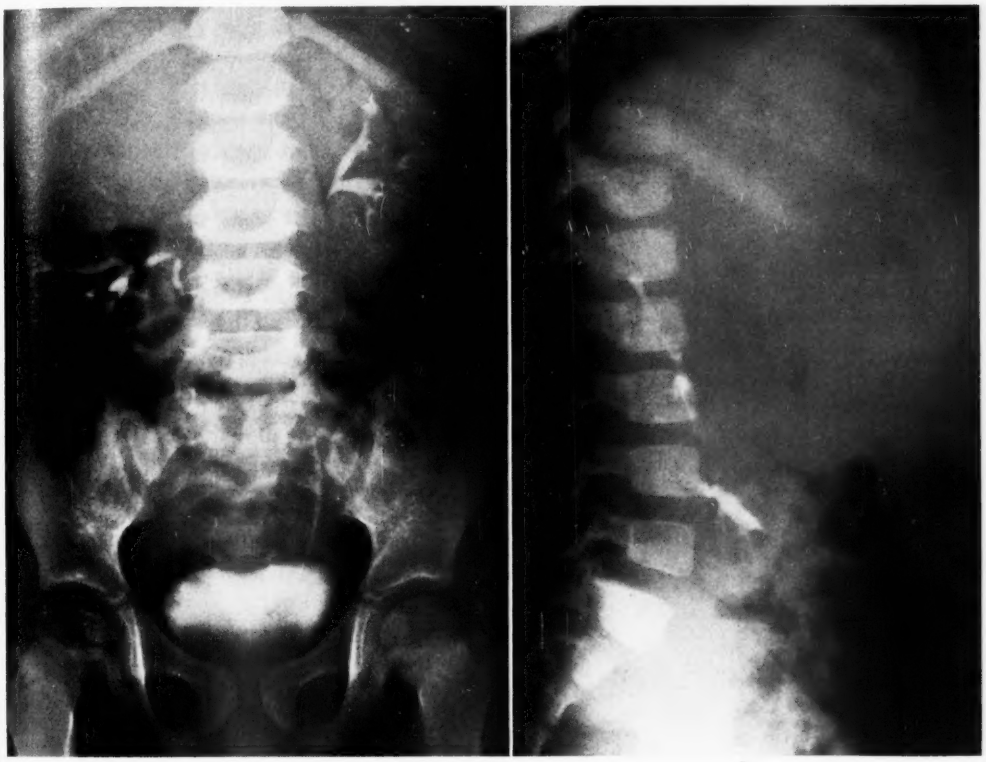
TABLE II.—SUMMARY OF CASES

Case Age, yrs. Sex	Symptoms and duration	Physical findings	Laboratory findings	X-ray findings	Operation	Hormonal adjuvants	Gross	Microscopic	Result	Comment
					BENIGN					
1 21 F	Hirsutism of face, male pubic hair since 12 yr.; accentuation of virilization for 1 yr.	Feminine body habitus, but well muscled; facial hair; male pubic hair	—	Perirenal air revealed tumor on right	Excision (flank)	—	55 gm. yellow tumor	Giant nuclei, pleomorphism; no vein or capsular invasion, no mitoses	Living and well 7 yr.	Virilizing. Signs and symptoms disappeared. Had normal baby 6 years postoperatively
2 19 F	Hirsutism, 2 yr. Weight loss, 6 mo. Amenorrhea, voice change	Hypertrichosis, underdeveloped breasts, enlarged clitoris, BP 110/90	RBC 5.0M WBC 9,600 Allen test 4+ 17KS 114-393 mgm./24 hr.	IVP distortion of right renal pelvis	Excision right tumor (abdominal)	A.C.E.	10 x 10 cm. soft brownish tumor	Uniform cells, well encapsulated, no mitoses or necrosis	Living and well 1 yr.	Virilizing. 20 days postoperative, 17 KS was 12 mgm./day
3 38 F	Amenorrhea, obesity 4 yr., hirsutism, deepening voice, acne	Obesity, plethora, acne, increased hair of trunk and face, enlarged clitoris. BP 150/90	RBC 6.1M; Hb. 17 gm. % FBS 89 mgm. % 17-KS 33.9–73.6 mgm./24 hr. Allen test neg. Formald. steroid 0.3 to 2.5 mgm./24 hr. Elect., normal	Laminograms suggest left adrenal tumor	Excision left tumor (flank)	Cortisone and DOCA	Spherical reddish-brown, 6 x 6 x 3 cm. 70 gram tumor	Uniform cells, resemble zona fasciculata; atrophic cortical tissue attached to tumor, tumor well encapsulated	Living and well 3 yr. 4 mo. postoperatively	Mixed syndrome, predominantly virilizing. 3 yr. postoperative, 17KS 9.5 mgm. 17-OHCS 9.6 mgm.
4 32 F	Full face, increased hair growth, weakness for 9 mo.	Obesity of trunk, "buffalo hump" plethora, purple striae, BP 150/100	Hb. 15.5 gm. FBS 302; 108 mgm. % K, Na normal 17-KS 9.7 mgm./24 hr. Formald. steroid 2.3 mgm./24 hr.	Tumor not revealed on plain films or IVP	Excision left tumor (abdominal)	ACE and cortisone	2.5 cm. spherical yellow tumor, 10 gm.	Regular cells, well encapsulated, no mitoses; atrophic adrenal tissue attached to tumor	Living and well 5 yr.	Cushing's type
5 1½ F	Rapid growth 6 mo. Pubic hair 3 mo.	Pubic hair with male distribution, clitoris and labia enlarged	Hb. 16.9 gm. Elec.—normal Gluc. tol.—normal 17KS 51 mgm./24 hr. Pregnanediol 14 mgm./24 hr. Allen test ++++	IVP shows left kidney depressed	Excision left tumor (abdominal)	DOCA and ACE	8 x 10 cm. yellow tumor	Giant nuclei, pleomorphism; no capsular or vein invasion, no mitoses, no necrosis	Living and well 9 yr.	Virilizing
6 3½	Excess weight 1 yr. Hirsu-	Florid face, acne, central	Hb. 14.09, RBC 5.0M		Excision,	ACE	7 cm. spherical	Original report benign ade-	Died 30 hr.	Cushing's type

Allen test ++++										
6 3½ F	Excess weight 1 yr. Hirsutism 9 mo.	Florid face, acne, central obesity, hypertrophied clitoris BP 230/50, palpable tumor	Hb. 14.09, RBC 5.0M WBC 14,350, FBS 65 mgm. % 17 KS 1.2 mgm./24 hr. Na pregnanediol glucuronidate 10 mgm./24 hr.	—	Excision, right (flank)	ACE	7 cm. spherical yellow tumor, well encapsulated	Original report benign adenoma, slides lost and not available for review	Died 30 hr. postoperatively. No autopsy	Cushing's type
MALIGNANT										
7 54 M	RUQ abdominal pain 5 yr.	RUQ mass	—	Displacement of hepatic flexure, IVP normal	Excision right adrenal tumor (abdominal)	None	15 x 10 x 8 cm., 900 gm. yellow tumor	Necrosis, mitoses, vein invasion; normal adrenal cortical tissue attached to tumor	Pulmonary metastases 2 yr.	Nonfunctioning
8 38 F	Mass LUQ, 3 yr. Loss of weight and strength	Huge mass LUQ, dilated abdominal veins (preop. diagnosis, carcinoma of kidney)	—	Depression left kidney on IVP	Palliative removal (abdominal). Invasion of diaphragm	None	Cellular masses of tissue	Mitoses, vein invasion, bizarre nuclei	Dead 2 yr. 9 mo.	Nonfunctioning
9 73 M	Pain in hip, weakness of leg, 60 lb. weight loss	BP 135/90, no endocrine stigmas, signs of pneumonia. Subcutaneous nodule of scalp	—	Pneumonia, pulmonary metastases, spinal metastases	None	—	—	Autopsy, carcinoma of right adrenal with invasion of adrenal vein and vena cava. Metastatic in brain, lymph nodes, liver, and kidney. Contralateral adrenal not atrophic	—	Nonfunctioning
10 41 F	Hypertension 14 mo., Amenorrhea 10 mo.	Obesity, hirsutism, acne, pedal edema. BP 175/100	17-KS 100 mgm./24 hr. 11-OCS 7.5 mgm./24 hr. Elect., normal	—	Excision (flank)	—	Large tumor with invasion of kidney	Necrosis, mitoses, vein invasion, bizarre nuclei, capsular invasion, invasion of kidney. Autopsy: metastatic to liver, lung, lymph nodes. Local recurrence, marked atrophy of right adrenal	Dead at 10 mo.	Cushing's syndrome
11 3 F	—	Moon face, hirsutism, enlarged clitoris, obese, osteoporosis	—	—	Excision	—	—	Necrosis, mitoses, bizarre nuclei	Operative death	Mixed syndrome, predominantly Cushing's (outside case)
12 12 M	Weight gain 25 lb. in 8 months, acne, precocity	Pubic hair, adult penis, plethora, BP 130/90	Hb. 15.6 gm. Elec.—normal 17 KS 93.9 mgm./24 hr. 17 OHCS 44.1 mgm./24 hr. FBS normal	Calcified tumor, displacement of kidney	En bloc resection of tumor, kidney, and spleen, (thoracoabdominal)	Cortisone	Tumor thrombus in adrenal vein; 940 gm. yellowish brown tumor with gross invasion of capsule	Necrosis, mitoses, vein invasion, calcification, capsular invasion, giant and bizarre nuclei	Dead 6 mo., persistent tumor and pulmonary metastases	Virilizing. P.O. fall in 17-KS to 4.9 mgm./24 hr.; at 4 mo. up to 17.8 mgm.

TABLE II.—SUMMARY OF CASES (Continued)

Case Age, yrs. Sex	Symptoms and duration	Physical findings	Laboratory findings	X-ray findings	Operation	Hormonal adjuvants	Gross	Microscopic	Result	Comment
MALIGNANT (Continued)										
13 7 mo. F	Left abdominal mass for 2 months	Mass left abdomen, obesity, preop. diagnosis—Wilms' tumor	RBC 5.47M Hb. 11.1 gm. % WBC 21,300	Depressed left kidney on pyelogram	Excision of left tumor and kidney (abdominal)	None	195 gm. pale pinkish-tan tumor	Necrosis, mitoses, vein invasion. Autopsy: metastases to lymph nodes and lung, atrophy of right adrenal, Crooke's cells in pituitary	Operative death	Hypercorticism not recognized preoperatively; however, Crooke's cells at autopsy indicate Cushing's type of adrenal overfunction
14 23 mo. F	Pubic hair, 7 mo.	Pubic hair, mass RUQ, clitoris slightly enlarged, BP 102/60	Hb. 8.7 gm. WBC 15,800 Elect.—normal Dehydroisoandrosterone 0.62 mgm./ml. urine	Calcification above right kidney, bone age 7 yr.	Excision right tumor (abdominal)	Cortisone, ACTH	15 x 5 cm., 920 gm. orange yellow tumor	No mitoses; vein invasion and bizarre nuclei present. Autopsy: tumor thrombus in vena cava, right heart and right pulmonary artery, multiple lymph node metastases. Left adrenal 4.5 gm., normal histologically	Died suddenly 3 mo. p.o.	Virilizing
15 17 mo. M	Obesity, 5 mo.	Moon face, acne, obesity, striae, hirsutism, BP 155/85	Hb. 15.4 gm. WBC 29,100 Elect.—normal 17 KS 3.7 mgm./24 hr. 17 OHCS 10.2 mgm./24 hr.	Soft tissue mass, displacing left kidney; bone age 12 mo.	Excision left tumor (thoracoabdominal)	Cortisone, ACTH	Spherical 8 cm. yellow tumor	Some pleomorphism and occasional giant nucleus. No mitoses or vein invasion. Capsule invaded at one point (see text)	Living and well 10 mo.	Mixed syndrome, predominantly Cushing's. At 10 mo. p.o., 17KS 1.04 mgm., 17-OHCS 1.4 mgm.
16 56 F	Mental changes, 8 wk. acne, bruisability, hirsutism	Wasting of extremities, ecchymoses, LUQ mass, BP 190/120	17 KS 73.0 mgm./24 hr. 17 OHCS 108 mgm./24 hr. Hb. 16.5 gm.; Na 148.6; FBS 139 mgm.; K 3.9; Cl 86 CO_2 25 mEq./1	Pulmonary metastases, soft tissue mass LUQ	Palliative excision tumor (thoracoabdominal)	Cortisone, hydrocortisone	Spherical 10 cm. yellow tumor, 290 gm.	Capsular invasion, vein invasion, and mitoses. Atrophic adrenal cortical tissue present. Liver metastases more undifferentiated than primary tumor	Operative death, no autopsy	Pure Cushing's. Chromatography of extract of tumor, compounds S and F



a b

FIG. 3. a and b, Pyelograms showing displacement of right kidney due to adrenal carcinoma.

determinations were done, 5 of them, regardless of predominant clinical syndrome had increased excretion of both 17-ketosteroids and 17-hydroxycorticosteroids. In 1 case with Cushing's syndrome the 17-ketosteroid value was normal. Of interest is Case 12, that of a 12 year old boy presenting with precocious puberty. The only Cushing's features were weight gain and fullness of face. The 24 hour urinary 17-ketosteroid value in this case was 93.9 milligrams and the 17-hydroxycorticosteroid value was 44.1 milligrams. Since hormones in the 17-hydroxycorticosteroid group are not metabolites of androgens, it is possible that Cushing's features had not yet become fully developed from a polyhumoral tumor. On the other hand, Case 16 was of a patient with Cushing's syndrome who exhibited no androgenic features though urinary 17-ketosteroid excretion was 73 milligrams per day. The 17-hydroxycorticosteroid excretion was 108 milligrams per day. Most of the urinary 17-ketosteroid could have been metabolite. Chromatography of extracts of this tumor revealed large amounts of compounds S and F.

PATHOLOGIC EXAMINATION

Among the problems in the pathologic evaluation of adrenal cortical tumors are the difficulty in distinguishing benign neoplasms from apparently nonneoplastic nodular lesions and the difficulty in some cases of distinguishing a benign from a malignant tumor.

About one-third of persons coming to autopsy have nodular lesions of some sort arising in the adrenal cortex. The most frequent variety exhibits small or minute non-

FIG. 4. Benign adrenal tumor, showing encapsulation and homogeneous surface.

encapsulated nodules which may be multiple. The intervening cortex is normal. These nodular adrenals do not present clinical problems and are not known to be associated with abnormal function. Occasionally the hyperplastic adrenal cortex in the "pituitary type" of Cushing's syndrome will exhibit gross nodularity. These nodules are seldom larger than 1 or 2 centimeters, while the true adenomas are generally much larger.

The benign true neoplasms in our series were differentiated from the previously described cortical nodules by the presence of complete encapsulation (Fig. 4), derangement of architectural pattern, and larger size. In addition, the cells in the tumors, while most frequently identifiable as of adrenal cortical origin, differed in form, size, and staining quality from the cells in adjacent uninvolved adrenal cortical tissue.

The differentiation between benign and malignant neoplasm can be made with facility in most cases. However, a few present problems. For instance, large bizarre nuclei (Fig. 5), which in tumors in other sites might suggest malignancy, are found in well encapsulated tumors and are not incompatible with long survival following removal (Cases 1 and 5). If other unfavorable pathologic stigmas are absent, the tumors containing giant bizarre nuclei may be associated with a benign course. On the other hand, tumors with fairly regular nuclei, but with capsular invasion (Fig. 6) or invasion of veins (Fig. 7) are most often associated with a malignant course. We consider certain criteria of malignancy to be frequent mitoses, venous invasion, and capsular invasion. Accessory findings which may be helpful in differentiating benign and malignant tumors are necrosis, hemorrhage, calcification, pleomorphism, and nuclear atypia, which all occur more commonly in the carcinomas. Some pathologic characteristics of tumors in our cases are shown in Table II.

At autopsy, 3 patients had large tumor thrombi in the vena cava, 1 of which had produced sudden death by massive embolization of tumor to the right side of the heart and pulmonary artery. Metastases have occurred in this series predominantly in regional lymph nodes, lungs, and liver.

On 8 occasions histologic examination was made of uninvolved adrenal cortical tissue, either of a fragment attached to the tumor or of the contralateral adrenal at autopsy. The 2 examples from persons with nonfunctioning carcinomas were both of normal thickness and architecture. The contralateral adrenal of a 2 year old girl with a virilizing carcinoma weighed 4.5 grams and histologically did not appear atrophied. In 5 other instances, the uninvolved adrenal cortical tissue was atrophied. Four of these were from patients with Cushing's syndrome, and 1 was from a patient with a mixed syndrome which was chiefly androgenic. The following case illustrates some of the consequences of this atrophy.

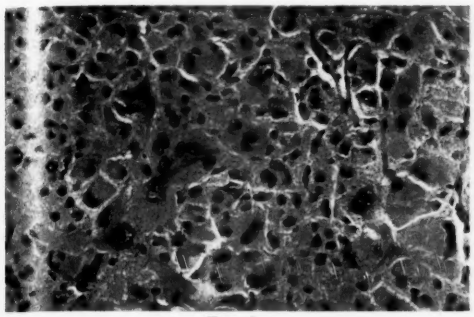


FIG. 5.

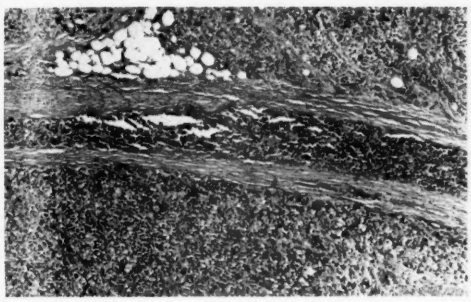


FIG. 6.

FIG. 7.

FIG. 5. Giant and bizarre nuclei in an adrenal cortical tumor. This finding does not necessarily indicate that the tumor is malignant.

FIG. 6. Invasion of capsule by adrenal carcinoma, with extension into fat. This does not occur in benign tumors.

FIG. 7. Adherent tumor thrombus in a vein, evidence that the tumor is malignant.

CASE 13. A 7 month old female infant entered the hospital because of a mass in the abdomen of 1 month's duration. Although the child was noted to be obese, hypercorticism was not suspected. The preoperative diagnosis was Wilms' tumor. No preoperative steroid therapy was administered. At operation, a large tumor involving the left adrenal and superior portion of the left kidney was removed en bloc with the kidney. Removal was thought to be grossly complete. In spite of blood transfusions, the child died in shock 3 hours following operation.

The pertinent findings at autopsy were: marked atrophy of the contralateral adrenal cortex which was reduced to about one-fourth of normal size (Fig. 8), metastases to a left upper abdominal lymph node and to lung, and hyalinized basophiles (Crooke's cells) in the adenohypophysis (Fig. 9). The Crooke's cells are pathognomonic of hypercorticism (3) even though the syndrome had not been recognized clinically.

By microscopic examination, it is not possible with present techniques to characterize the functional capacity of adrenal tumors. The nonfunctioning, the virilizing, and the Cushing's syndrome-producing tumors appear not dissimilar. The only suggestion of such a difference in our cases was that in the tumors from cases of Cushing's syndrome, the cells tended to be arranged in cords and clumps faintly reminiscent of zona fasciculata and glomerulosa (Fig. 10) more frequently than in the virilizing tumors.

OPERATION AND OPERATIVE RESULTS

Most of the tumors in this series were explored by transabdominal and flank incisions. We now prefer the thoracoabdominal approach in cases in which the tumor has been lateralized prior to operation, since it offers better exposure and consequently better prospects of removing the tumor intact and

FIG. 8.

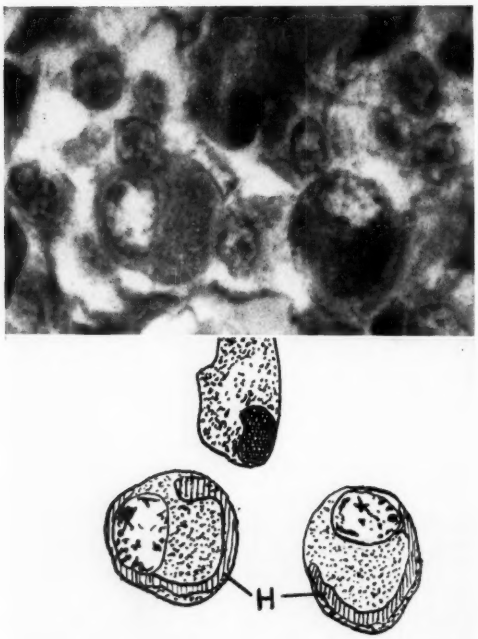


FIG. 9.

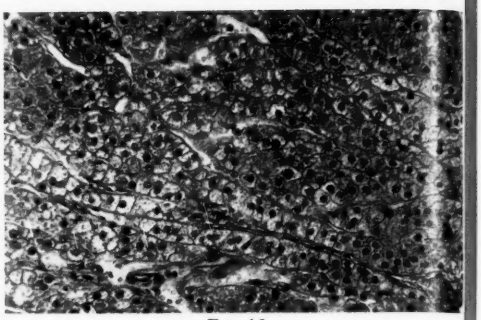


FIG. 10.

FIG. 8. Above, Normal adrenal from a 5 month old girl. Below, Markedly atrophic adrenal which was contralateral to a functioning carcinoma in a 7 month old girl (Case 13), same magnification.

FIG. 9. Hyalinized pituitary basophiles (Crooke's cells) from Case 13. These are pathognomonic of hypercorticism. In the drawing, *H* identifies the concentrically located hyaline material in the 2 basophiles.

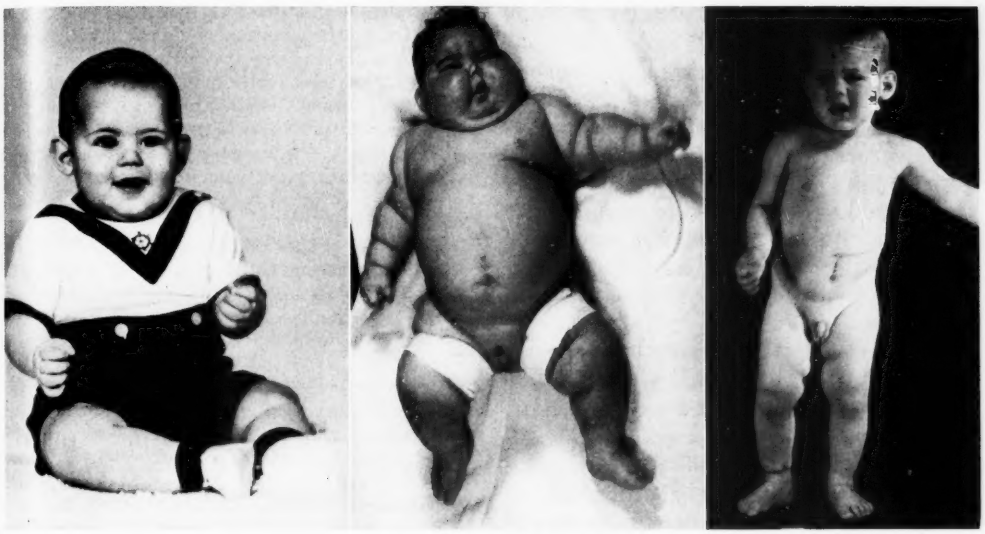
FIG. 10. Pattern reminiscent of zona fasciculata in a benign tumor associated with a mixed syndrome (Case 3)

removing en bloc any adjacent tissue (diaphragm, tail of pancreas, kidney) that might be invaded. In cases of hypercorticism without clinical diagnosis of tumor, bilateral flank exploration is preferred.

The availability of commercial steroid hormones for substitution has greatly improved operative results. In Table I, it is seen that in the 1930 to 1949 series collected by Rapaport and associates, the mortality rate following removal of cortical tumors in Cushing's syndrome was exorbitantly high (56.3 per cent) when substitution therapy was lacking or inadequate. Although the 1950 to 1955 series includes some cases done in prior years when cortisone was not available, most of the reduction in mortality (to 20.6 per cent) is attributed to better replacement therapy. For details regarding substitution therapy see Thorn's monograph.

Death following operation in Cushing's syndrome may occur immediately in a shock-like state. Our 4 operative deaths occurred within 30 hours; 3 were associated with inadequate steroid therapy. The fourth patient, who had massive hepatic metastases, was believed to have had adequate replacement. No deaths due to operation occurred in patients with androgenic tumors in our series.

Most often the dosage of postoperative steroid replacement therapy can be gradually



a b c

FIG. 11.

FIG. 11. a, Case 15, at age 7 months, before the development of hypercorticism. b, Same child at age 17 months, at the height of symptoms. c, At age 27 months, all stigmas of hypercorticism have disappeared.

FIG. 12. Tumor from Case 15. The capsule is thin. On cut surface small areas of necrosis are seen.

FIG. 13. Microscopic appearance of tumor, Case 15, showing moderate pleomorphism in a very cellular tumor.

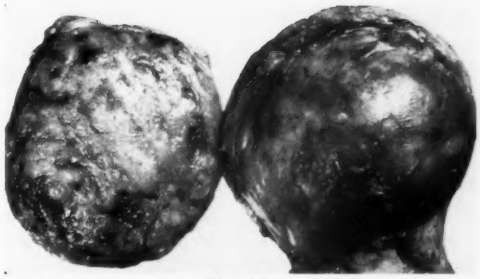


FIG. 12.

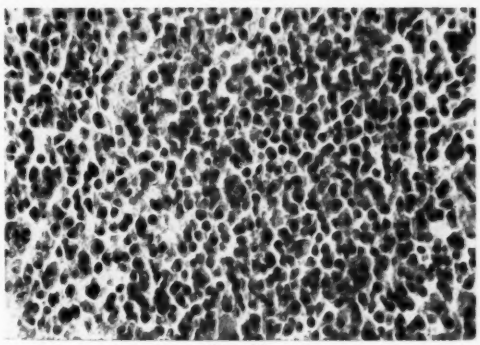


FIG. 13.

diminished and generally discontinued within 2 weeks, particularly in patients with mild Cushing's syndrome and in those with the androgenital syndrome. It is not believed necessary to employ ACTH to stimulate the remaining hypofunctioning contralateral adrenal, since spontaneous recovery occurs. Occasionally in persons who have had severe Cushing's syndrome one sees a prolonged postoperative illness which Cope attributes to acute nutritional deficiency. One of our patients (Case 15) exhibited stupor, fever, diarrhea, and vomiting beginning about 1 week after cortisone was discontinued. He recovered after reinstituting small doses of cortisone for 2 weeks.

The mortality rate following excision of adrenal tumors is much lower in the adrenogenital syndrome than in Cushing's syndrome (Table I). This is probably associated with the fact that atrophy of the contralateral adrenal occurs less commonly (29 per cent in the adrenogenital syndrome and 73 per cent in Cushing's syndrome), and consequently the need for replacement therapy is

less and the results of inadequate therapy may not be so disastrous.

The long term results following removal of benign tumors are good, with practically uniform reversion to normal physical status in those cases reported. Five of our 6 patients with benign tumors are well at 1, 3, 5, 7, and 9 years, and 1 died following operation. One of the patients has residual hypertension of moderate degree, but other physical and chemical evidences of her hypercorticism have regressed. The reported results following removal of malignant adrenal tumor are dismal, although occasional long term survival in good health has been recorded. These survivors are all patients whose tumors were localized and fairly well encapsulated, but in whom histologic diagnosis of malignant tumor was made. Of our 10 patients with malignant tumor, 9 were operated on, 3 died postoperatively, and 5 have died of metastatic disease from 3 months to 3 years after operation. Only 1 is alive and well, with a 10 months' follow-up. Because of the rarity of successful results in Cushing's syndrome due to adrenal carcinoma, this case is reported in detail.

CASE 15. A 17 month old white boy entered on January 17, 1956, with obesity and hirsutism which had been developing for 5 months prior to admission. The boy had sat at table, eating adult portions of adult food. Initially, because of his appetite, obesity, and ruddy complexion he had been considered to be unusually healthy and advanced by his parents, until the obesity and ruddiness reached grotesque proportions (Fig. 11a and b).

On admission he weighed 47 pounds. The face, extremities, and trunk were markedly obese. Scalp hair was dark and kinky. Fine black hair was present generally over the body, but particularly on the forehead, jowls, back, and pudendal area. There was acne of the face and trunk and purplish striae of the thighs. Blood pressure was 150/90. The red cell count was 5.37 million, with 12.8 grams per cent hemoglobin. The white cell count was 29,100, with 1 basophilic, 4 stab, 57 segmented, 28 lymphoid, and 10 mononuclear cells. Fasting blood sugar was 105 milligrams per cent. Plasma electrolytes showed: sodium 136.9, potassium 3.5, chloride 104, carbon dioxide 27.0 milliequivalents per liter. Urinary 17-ketosteroid excretion was 3.7 milligrams per 24 hours (normal for infants is less than 1 mgm.), and urinary 17-hydroxycorticosteroid excretion was 10.2 milligrams per 24 hours (normal for infants probably less than 1.5 mgm.). Roentgen examination showed a bone age of 12 months. Plain films of the abdomen showed a spherical left suprarenal tumor. Preoperatively, cortisone acetate was begun 3 days prior to operation. Through a left thoracoabdominal incision, a discrete tumor 8 centimeters in diameter was removed intact on February 3, 1956. At operation there was no adherence to adjacent viscera.

On the day of operation he received 100 milligrams of cortisone acetate intramuscularly and 150 milligrams of hydrocortisone intravenously. Cortisone dosage was gradually diminished and was discontinued on the twelfth postoperative day, and he was discharged.

The tumor weighed 140 grams. There was no gross vein or capsular invasion. On cut surface, it was yellow and homogeneous (Fig. 12). Microscopically, it was composed of relatively small cells with scanty cytoplasm and little intervening stroma (Fig. 13). The nuclei showed moderate variation in size, but there were no giant nuclei. Small areas of necrosis with fine calcification were present. Mitoses were present but infrequent. No microscopic evidences of vessel invasion were seen but tumor had penetrated the thin capsule at several sites. Because of the capsular invasion and mitoses, it is believed that this was a malignant tumor.

He was readmitted on March 19, 1956, because of stupor, fever, and diarrhea. He seemed to be having a great deal of pain in his back. He was dehydrated and acidotic (Na 147.1, K 3.4, CO_2 23.4, Cl 93 mEq./l., urine *p*H 4.5, acetone +). Cortisone was reinstituted and symptoms gradually subsided. Cortisone was again discontinued on April 25, 1956.

He was last seen October 17, at which time he weighed 28½ pounds and appeared to be normal in all respects (Fig. 11c). Blood pressure was 90/60. Scalp hair, previously kinky and black, is now straight and brown. Body hair has disappeared. Urine 17-ketosteroid was 1.04 milligrams and 17-hydroxycorticosteroid was 1.4 milligrams per day.

SUMMARY AND CONCLUSIONS

1. Clinical and pathologic features of 16 cases of adrenal tumor are reported.

2. The clinical effects of hormonally active tumors may simulate those resulting from bilateral adrenal cortical hyperplasia and are attributable to one or more of the specific steroid hormones of the adrenal cortex.

3. Atrophy of the remaining normal adrenal cortex is found frequently in Cushing's syndrome due to adrenal tumor. This results in postoperative adrenal cortical insuf-

ficiency with a high operative mortality rate upon the removal of the tumor unless adequate preoperative and postoperative substitution therapy has been instituted.

4. Malignant tumors (10 in our series) have histologic criteria which tend to differentiate them from the benign (6 in our series). Malignancy usually is associated with pleomorphism, giant and bizarre nuclei, frequent and sometimes atypical mitoses, hemorrhage, necrosis, and calcification. Absolute criteria of malignancy are invasion of veins, invasion into and through the capsule, and distant metastases.

5. The long term follow-up results in cases of benign tumor are good. The 5 patients who survived removal of benign tumor are all well, from 1 to 9 years following operation. With malignant tumor the results are very poor, only 1 of 10 patients in our series having a prospect of cure (10 months follow-up).

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BLOOD VOLUME FLUCTUATIONS DETERMINED BY RADIOISOTOPES OF CHROMIUM AND RADIOACTIVE IODINATED SERUM ALBUMIN

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THE CIRCULATING BLOOD VOLUME is a dynamic quantity. It is capable of undergoing rapid changes. It was the purpose of this study to investigate some of the factors responsible for fluctuations in the blood volume and determine how they are reflected in the isotope dilution technique. It was believed that if changes in blood volume could be measured reliably by the isotope technique then the determinations of serial blood volumes would prove to be of value in several clinical conditions.

METHODS

Three to 4 microcuries of radioactive iodinated serum albumin (RISA) diluted in 20 cubic centimeters of saline and a 20 cubic centimeter suspension of group O, Rh negative red cells tagged with radioactive chromium (Cr^{51}) containing 20 microcuries were injected either individually or simultaneously into a peripheral vein. Ten cubic centimeters of blood specimens were withdrawn through an indwelling catheter in the femoral vein into heparinized syringes at desired intervals. Repeated doses of the isotopes could be injected through the indwelling catheter, thus allowing the determination of the blood volume on the basis of the new dose administered. This new volume could then be compared to the volume determined by the preceding dose of isotope.

When single isotopes were used the specimens were counted as whole blood, and the blood volume calculated according to the following formula:

$$\text{Blood volume} = \frac{\text{Counts of standard} \times \text{c.c. administered}}{\text{Counts of specimen} - \text{background}}$$

When both isotopes were used together the whole blood was counted, then centrifuged, the plasma counted, and the hematocrit determined in duplicate by a microhematocrit technique. The following calculations were made:

1. $$\text{Plasma volume} = \frac{\text{Counts of RISA standard} \times \text{c.c. administered}}{\text{RISA count in plasma} - \text{background}}$$

2. $$\text{RISA count in whole blood} = (1.0 - \text{hematocrit}) \times \text{plasma RISA count}$$

3. $$\text{RISA blood volume} = \frac{\text{RISA plasma volume}}{1.0 - \text{hematocrit}}$$

4. $$Cr^{51}\text{ blood volume} = \frac{\text{Counts of } Cr^{51} \text{ standard} \times \text{c.c. administered}}{\text{Total count in whole blood} - \text{RISA count in whole blood}}$$

RESULTS

Fluctuations in blood volume in normal subjects. The blood volume measured with a single injection of Cr^{51} remained fairly constant for a 24 hour period. Repeated injections of Cr^{51} confirmed the results. Increases of as much as 500 cubic centimeters were noted following meals or ingestion of large quantities of fluids. In approximately 3 to 4 hours, the blood volume returned to its original level. Volumes taken at night were somewhat higher, probably because of relative hypotension and decreased renal filtration.

The blood volumes measured with RISA failed to show the stability of those measured with Cr^{51}. As a rule, the volumes tended

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to become progressively larger with each measurement, probably representing a "leak" of isotope. In addition, the volumes were not appreciably affected by ingestion of food and liquids.

The effect of intravenous fluids on the blood volume. Several patients were given infusions of either physiologic saline solution or 5 per cent glucose in distilled water. It was found that with infusions of as little as 500 cubic centimeters an increase in the blood volume could be detected. This increase was transitory, and in 2½ to 3 hours the blood volume would return to its original level. Even with rapid infusions of saline solution the blood volume seldom increased in accordance with the amount infused. On the other hand, with rapid infusions of glucose, the blood volume often temporarily increased in an amount greater than that given the patient. This apparently was a reflection of the osmotic effect of the glucose. With either type of infusion, there was a temporary fall in the hematocrit corresponding to the temporary increase in the blood volume. These changes were more clearly demonstrated with Cr^{51} than with RISA (Fig. 1).

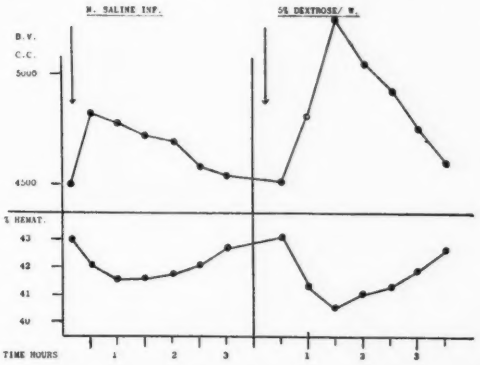

FIG. 1. Blood volume determinations with Cr^{51} tagged red blood cells. Effect upon blood volume and hematocrit by the intravenous administration of 500 cubic centimeters of physiologic saline solution and 500 cubic centimeters of 5 per cent dextrose in distilled water, rapidly over 30 minutes.

The effects of hypotension on the blood volume. Blood volume determinations taken before and after premedication with morphine, before and after induction of anesthesia with pentothal, and before and after reducing the blood pressure with arfonad® demonstrated an increase in the Cr^{51} volumes if the pressure had been significantly lowered. There was an associated fall in the hematocrit. In all instances there was good correlation between hypotension and increases in the Cr^{51} blood volume. When hypertension was induced with neosynephrine the blood volume decreased and the hematocrit increased.

The blood volume as measured with RISA demonstrated minimal fluctuations with hypotension induced by any of these methods. An interesting observation was noted: When both isotopes were used together, the RISA volumes tended to be 10 to 40 per cent greater than the Cr^{51} volumes. When hypotension was induced, the Cr^{51} volumes increased and tended to equal the RISA volumes. The patients with the largest differences in the Cr^{51} and RISA volumes developed hypotension with premedication and induction of anesthesia. Usually these changes were encountered in patients afflicted with chronic debilitating diseases (Figs. 2 and 3).

The effect of bleeding of 25 per cent of the blood volume. Serial blood volume determinations with Cr^{51} were made in several cases during and following rapid bleeding of approximately 25 per cent of the blood volume.

In some cases this amount of blood loss did not alter the blood volume when 1 injection of isotope had been used. There was also no change noted in the hematocrit. These findings are accounted for by the fact that the blood removed from the patient contained the same distribution of isotope as the blood remaining in the patient. If another dose of isotope was given after bleeding and a new blood volume determined, it would accurately measure the decrease in the blood volume due to the blood removed. When these cases were followed with determinations for 48 hours, a gradual hemodilution was noted by an increasing blood volume and a falling hematocrit.

In a few cases, a different pattern was encountered. The blood volume taken im-

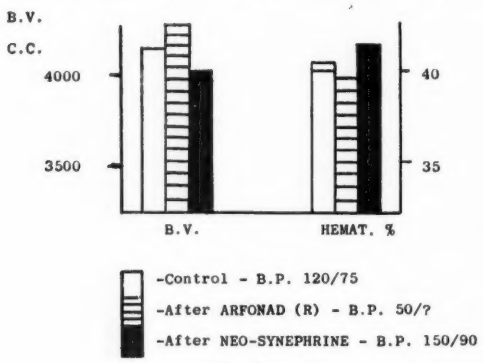

FIG. 2.

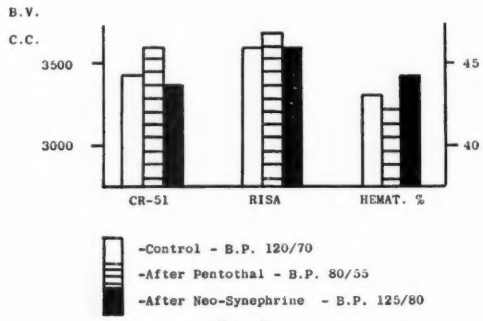

FIG. 3.

FIG. 2. Blood volume determinations with Cr^{51} tagged red blood cells. Note the increase in the blood volume and the fall in the hematocrit when the blood pressure was lowered with arfonad. The reverse is true when the blood pressure is elevated with neosynephrine.

FIG. 3. Blood volume determinations with Cr^{51} red blood cells and RISA. Note the increase in blood volume as measured by Cr^{51} and the fall in hematocrit when the blood pressure fell with pentothal induction. With neosynephrine the reverse occurred. These changes in blood volume are not detected when measured with RISA.

mediately after the bleeding demonstrated a decrease in the count, indicating a more prompt hemodilution. There was also a fall in the hematocrit. When another dose of isotope was given after bleeding, the newly determined blood volume would not be decreased proportionately to the amount of blood removed. It was found to be reduced about two-thirds of the total amount taken from the patient, thus again indicating that some hemodilution had taken place.

Seldom with this amount of bleeding was there any significant change in the blood pressure, the patients being kept flat in bed during the tests. When the pattern indicating a rapid hemodilution was encountered, there was usually a slight hypotension. These patients became restless and often did not lie calmly during the studies. Perhaps the hypotension was responsible for the appearance of the prompt hemodilution.

When vasodilators were administered following the bleeding, a marked hypotension occurred and the blood volume rapidly increased with a corresponding fall in the hematocrit. This effect could be reverted with vasopressors, with a decrease in the blood volume and a rise in the hematocrit (Fig. 4).

Serial studies of blood volume during the operative and postoperative period. Many cases were studied with both isotopes during the operative and postoperative period in an attempt to evaluate the accuracy of blood volume determinations during the operative trauma.

The data obtained when RISA was used could not be considered reliable. There was a tendency for progressive increases in the RISA blood volumes. These increases occurred more rapidly than those seen when serial determinations were done in normal patients. The operative trauma with associated leakage of the tagged albumin probably accounts for these rapid increases in the RISA volumes during surgery.

Serial volumes taken with multiple doses of Cr^{51} during the operative and postoperative period can usually be properly interpreted. As indicated before, blood volume determinations with this isotope increase when the blood pressure falls so that with premedication and induction of anesthesia, there may be an increase in the volume. Blood loss during surgery can be measured by the multiple dose technique. It is essential for the blood pressure to be stable. The patient must not be actively bleeding at the time or the isotope will be lost before distribution occurs. Fifteen minutes must be allowed from the time of administration of the isotope until a sample is withdrawn for counting. When these factors are considered, blood volume determinations, hematocrit, and red

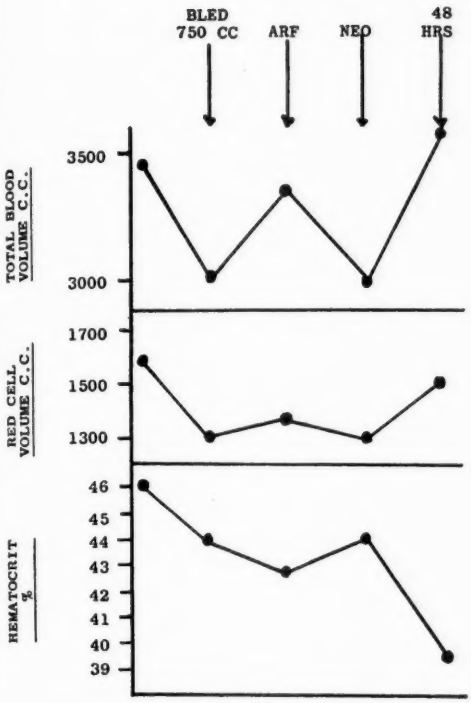

FIG. 4.

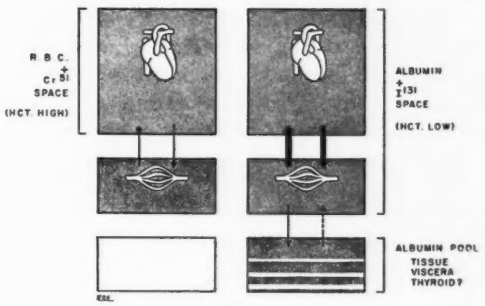

FIG. 5.

FIG. 4. Each blood volume determination indicated on the graph was performed by administering an additional dose of Cr^{51}. After bleeding 750 cubic centimeters, the blood volume decreased only 500 cubic centimeters. There was also a slight fall in the hematocrit. This indicated a prompt 250 cubic centimeter hemodilution. When the blood volume was reduced by hemorrhage, hypotension produced by administering arfonad caused a notable increase in the blood volume. Neosynephrine produced the opposite effect. In 48 hours hemodilution occurred so that the blood volume was actually higher than originally, while the hematocrit was decreased.

FIG. 5. Diagrammatic representation of the spaces measured by red blood cells tagged with Cr^{51} and RISA.

cell mass determinations follow a reliable pattern during surgery and during the postoperative period.

DISCUSSION

Cr^{51} tagged red cells and I^{131} tagged serum albumin measure two different spaces in the body. Figure 5 is a diagrammatic representation of these spaces. Cr^{51} measures the central circulating blood volume. This space has a higher hematocrit than the peripheral or capillary blood volume. With hypotension and vasodilatation there is a further dilution of the Cr^{51} tagged cells, for they become partially distributed in the peripheral blood volume. The increases found in the Cr^{51} blood volume with hypotension are probably a combination of this effect with some actual hemodilution of the central circulating blood volume. This technique does not allow interpretation of which factor is paramount in producing increases of the blood volume when vasodilatation occurs. Since these changes take place so rapidly and are easily reversed by vasoconstrictors, the dilution of the tagged cells by entering the peripheral volume is more likely the accountable factor.

RISA on the other hand measures a space 10 to 40 per cent larger than the Cr^{51} tagged red cells. This fact is represented in Figure 5 as measuring the central circulating blood volume and a portion of the peripheral volume. Changes in the arteriolar tone have little effect on the RISA volumes. RISA, however, apparently leaks into the albumin pool, and portions of it are no longer available to the circulation. This accounts for progressive increases in RISA volumes if taken over a period of hours. RISA, therefore, has no value for serial determinations. It is satisfactory only for single determinations which are taken soon after it is administered, before it begins to enter the albumin pool.

It was interesting to note that vasodilators increased the Cr^{51} blood volumes when administered following blood loss. This action again may represent hemodilution, but may well be only an escape of the Cr^{51} tagged cells into the peripheral circulating volume. From these studies it is difficult to evaluate if vasodilators have a true protective effect in blood loss by allowing more effective hemodilution.

SUMMARY

Studies of serial determinations of blood volume with Cr^{51} tagged red cells and RISA indicated that Cr^{51} is the more reliable medium. RISA is satisfactory only for single determinations, but has little value when repeated blood volume determinations are desired.

The blood volume when determined with Cr^{51} increases with hypotension irrespective of the cause of vasodilatation. This may be due to either hemodilution or an increased distribution of Cr^{51} tagged red cells. Various degrees of both are most likely responsible.

Blood loss of 25 per cent of the blood volume is usually followed by a gradual hemodilution. If hypotension occurs with this degree of blood loss, hemodilution apparently takes place rapidly.

ACUTE HEPATIC ISCHEMIA IN ACTH TREATED DOGS

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STUDIES ON LIVER ISCHEMIA are continuing to command attention in the development of more efficient approaches to liver tumors, in the surgery of trauma, and in attempts to understand the role the liver plays in shock.

It has been reported that dogs subjected to occlusion of the afferent blood supply of the liver for an hour die in shock when the vessels are released. Efforts have been made to attempt to increase the liver's tolerance to ischemia. In earlier experiments on liver ischemia, we had indications (14), as did Raffucci (25, 26) that ACTH was of value in prolonging the survival time. The current study was planned to investigate this problem further and to study certain biochemical changes. The period of ischemia was arbitrarily chosen at 1 hour.

Bernhard and associates have shown that hypothermia during hepatic ischemia is of great value, in that 25 out of 27 dogs survived a 1 hour period of ischemia. Increasing the blood supply to the liver after the ischemia by means of a reverse Eck fistula, and the use of antihistaminics both failed to increase survival in a prior study (14).

METHODS

Twenty-eight healthy, adult mongrel dogs, weighing 15.5 to 27 kilograms were used in this experiment, 13 being used as a control group and 15 were treated with ACTH. All the dogs were in the laboratory for at least 10 days prior to testing and were kept on a diet of bread, milk, Karo syrup, yeast, and horse meat. Preoperative medication consisted of 600,000 units of penicillin 4 hours before surgery, and morphine and atropine 1 hour before the procedure. The anesthetic was open drop ether. Sterile operative technique was observed. The abdomen was opened through a midline incision and the hepatic, gastroduodenal, and hepatic arteries proper were isolated and a ligature of heavy silk placed around them. A portacaval shunt was done according to Freeman's technique. The acute hepatic ischemia was then produced by ligating the portal vein close to the liver and immediately tying the loops around the arteries. One hour later the vessels were released by cutting the knots, and, in all cases, the vessels regained their patency. During surgery, 700 cubic centimeters of 10 per cent glucose in water were infused intravenously. Those in which blood sugar and plasma pentose were studied were infused with normal saline.

The following determinations were done in duplicate on the peripheral blood in a number of the dogs: hematocrit, plasma inorganic phosphorus, total acid soluble phosphorus, alkaline phosphatase, nonprotein nitrogen, amino acid nitrogen, plasma pentose, blood sugar, and blood ammonia nitrogen. These determinations were run according to the following schedule: immediately prior to surgery, just before ligating the vessels, just before the release of the vessels, then at intervals of 15 minutes, 1 hour, 2 hours, and 4 hours after the vessels were released.

Whole blood was replaced in the same quantities as it was withdrawn. In all the dogs, rose bengal dye clearance was studied 2 days before surgery and in the survivors weekly, until the values returned to normal.

Penicillin, in the dose of 600,000 units daily, was given postoperatively during the first 4 or 5 days. Postmortem examinations were done on all the dogs. Survivors were sacrificed about 3 months after surgery.

The ACTH treated dogs received the hormone as follows: 50 milligrams intramus-

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cularly given 24 and 4 hours prior to surgery, 100 milligrams during surgery in the intravenous infusion, 50 milligrams intramuscularly 4 hours after surgery, and 25 milligrams intramuscularly 12 and 24 hours after surgery.

EXPERIMENTAL RESULTS

Of the 13 dogs in the control group submitted to 1 hour of liver ischemia, 12 died in a shock-like state in less than 12 hours; the other survived indefinitely and was apparently in good health as far as the appetite and weight were concerned. Blood studies in this lone survivor (rose bengal, alkaline phosphatase, and nonprotein nitrogen) returned to preoperative values within a month.

Of the 15 dogs in the ACTH treated group, 5 died in less than 12 hours. Their response to the ischemia and the autopsy findings were similar to the animals in the control group. Four of the 15 dogs survived from 36 hours to 15 days. Three of these developed liver necrosis, with 1 having necrosis of the head of the pancreas along with liver necrosis, and the 1 that survived 15 days died of pneumonia. Six of the ACTH group survived indefinitely, and 5 of them had normal livers when sacrificed. Alkaline phosphatase determinations were slightly elevated for a month and the rose bengal dye clearances were low for some time longer. The sixth surviving dog had a patent portacaval shunt and in spite of a good appetite, he lost 2 kilograms and had a fatty liver and a slight degree of fibrosis—findings which are commonly seen in the Eck fistula dog. The rose bengal dye clearance was around 50 in this dog, but was improving at the time it was sacrificed. The survival times are shown in Figure 1.

The gross appearance of the liver during surgery was observed in the two groups. When the vessels were ligated, the liver usually became pale and contracted to about half of its original size. When the vessels were released, the liver became engorged within in a few minutes. In the control dogs, the liver became very dark, whereas in the ACTH group, the color was usually a brownish red to bright red.

No major differences were seen in the blood pressure readings. In both groups, a sudden drop was noted within 4 minutes after release of the ligatures. This was followed by an increase almost to normal levels during the next half hour. A slow drop appeared 3 to 5 hours later in the dogs that died during the first 12 hours.

Within the first hour after surgery, the dogs regained consciousness, and most of them were able to stand and walk for a few minutes. Dogs which failed to survive became comatose and the pulse was thready with a marked tachycardia. The survivors were very weak for 1 or 2 days. The serum nonprotein nitrogen and phosphorus was usually increased and the blood sugar, pentose, and hematocrit values decreased. Most of the dogs accepted water the first day and milk on the second. The standard diet was started on the third day.

Both groups showed increased hematocrits 2 hours after ischemia, but no group differences were noted. Treated and control dogs also presented somewhat similar changes in the inorganic phosphorus levels in that before the ischemia there was a slight increase with a fall to below normal during the ischemia. Following the release of the vessels, there was another slight rise at 15 minutes which gradually fell over the 4 hour period to the preoperative level. The control animals had slightly higher levels than those treated with ACTH.

The plasma total acid soluble phosphorus is represented largely by inorganic phosphorus. The slightly higher values that were found in the ACTH treated dogs were due to the increase in the organic fraction.

Alkaline phosphatase was studied during the acute experiment in 5 dogs from the control group and in 3 from the ACTH treated group. Progressive increases were noted in the controls but no change was seen in the treated dogs. The survivor of the control group showed the same values as the ACTH

treated animals. These groups are too small to be of significance.

The plasma nonprotein nitrogen decreased during surgery and rose significantly after release of the vessels. No changes were noted in the dogs that recovered from the liver injury and survived.

Ammonia nitrogen in the blood increased progressively during the experiment in both groups and showed marked variation from one dog to the other. The highest values were found generally in the 4 hour sample and varied from 157 to 650 micrograms per 100 milliliters of blood. Normal fasting samples were from 30 to 70. Dogs with extremely high blood ammonia levels usually died but the reverse was not true since some dogs died in a few hours with levels of only 200 to 300 micrograms.

The plasma amino acid nitrogen was determined in 4 experiments and, in 3 of them, slightly increased values were found. These various determinations are shown in Tables I and II.

Blood sugar determinations were done in only 6 animals from the ACTH treated group and 1 from the control group. The results are shown in Table III. The fasting samples in the ACTH treated group were higher, but, in general, the same curve was seen. The hyperglycemia that developed when the vessels were released was maintained through the 2 hour sample. An infusion of 250 cubic centimeters of 10 per cent dextrose in water was started after the 4 hour samples were taken. This evidently did not change the survival time, as 3 out of 6 of the dogs that survived indefinitely did not receive dextrose at all.

Plasma pentose determinations were done in most of the dogs but the data were difficult to evaluate because: it was demonstrated that dextrose interfered as much as 4.8 milligrams for each 100 milligrams per cent; there were important variations of the blood sugar per se due to the ACTH and the surgical procedure; 17 dogs received dextrose infusion during surgery. In the dogs that were infused with saline, an increase

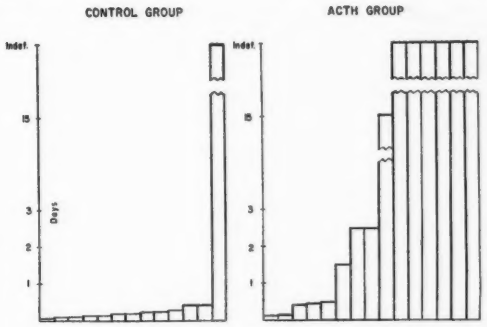

FIG. 1. Survival time of dogs with 1 hour of liver ischemia.

in plasma pentose parallel to that of the blood sugar was noted in many instances. The fasting plasma pentose level was higher in the ACTH treated animals than in the control group—6.96 and 5.1 milligrams per cent respectively. In dog 322, ACTH treated, the determination was done in whole blood, the fasting sample being as high as 23 milligrams per cent and the blood sugar 265 milligrams per cent.

The clotting time was investigated in a few instances and was found to be somewhat longer in the controls than in the ACTH group. A progressive tendency to hemolysis was also noted, particularly in the controls, but was not studied thoroughly. Tanturi has reported similar findings in fatal cases of experiments on hepatic artery ligation.

POSTMORTEM FINDINGS

In those dogs which died in a few hours, a dark, congested, and friable liver with patchy areas of necrosis was found. Often pale, yellowish areas were seen. The shunts were patent, and variable amounts of blood and lymph were present in the abdominal cavity. Hepatic necrosis was the major finding in the animals that survived from 1.5 to 2.5 days. No other gross pathologic findings were noted in the kidneys, adrenals, gastrointestinal tract, and chest. In the survivors from the ACTH treated group, 5 had normal livers, and the other had a fatty liver with

TABLE I.—BLOOD CHANGES IN THE CONTROL GROUP

Dog No.	Sex Weight, kgm. Rose bengal	Blood sample	Hematocrit	Total acid soluble phosphorus mgm. per cent	Inorganic phosphorus mgm. per cent	Alkaline phosphatase Bod. units per cent	Nonprotein nitrogen mgm. per cent	Intravenous infusion	Survival time	Comment
245	Male	B.S.	56	5.8	4.6		27	10%	4 hrs.	On post.: liver dark, congestive. In peritoneal cavity, no blood and very little free fluid
	21.9	15 min.	52	9.4	7.1		31	D/W		
		2 hrs.	61	5.5	4.0		45			
	130	4 hrs.	64		7.2					
251	Male	B.S.	45	3.7	3.5	0.6	27	10%	7 hrs.	Very little free fluid in abdomen on post. Liver dark, congestive
	18.5	B.I.	46	5.6	4.5	1.0	31.5	D/W		
		B.R.	46	4.7	3.8	1.2	29.5			
	126	15 min.	46	4.4	3.3	1.6	36.5			
		1 hr.	50	3.8	2.5	2.3	41			
		2 hrs.		2.8	2.1	2.5	50			
		4 hrs.	51	4.7	3.3	3.4	41			
250	Male	B.S.	42.5	4.9	3.4	2.3	29.5	10%	Indef.	Good recovery 1st 2 days only accepted water; 3rd day milk and meat. Blood studies normal in 3 wks. Sacrificed 3 mos. Normal liver. Latex rubber to bl. supply. No anatomic reason for its survival
	18.5	B.I.	46	5.8	5.0	2.2	24	D/W		
		B.R.	42	4.3	4.1	1.8	22			
	121	1 hr.	41	5.6	4.8	2.1	23			
		2 hrs.	40	5.4	4.0	2.2	24			
		4 hrs.	50.5	3.2	2.2	3.0	24.5			
263	Male	B.S.	38.5	4.0	3.3	2.6	33	10%	2.5 hrs.	Clotting became very poor after release of ischemia. 2 hrs. sample did not clot. Autopsy: more than 500 c.c. of blood in abdomen
	22.2	B.I.	32	9.6	8.4	2.5	27	D/W		
		B.R.	33	7.5	7.1	2.7	26			
	108	15 min.	33	8.2	8.2	3.3	47			
		1 hr.	32.5	7.9	7.1	4.7				
		2 hrs.	33	7.3	5.8	7.5	44			
278	Male	B.S.	50.5	5.1	4.7	6.2	30	10%	4 hrs.	After vessels were released clotting time was 30 min., and progressive hemolysis was noted in the samples. Terminal ammonia N.: 562 ugm. %. Autopsy: 100 c.c. of blood in abdominal cavity. No clots
	22.0	B.I.	57	5.9	4.7	4.6	25	D/W		
		B.R.		7.0	6.1	4.9	20			
	96	15 min.	53.5	9.4	8.0		29			
		1 hr.	54	9.1	8.2	11.5	28			
		2 hrs.	51.5	7.3	6.4	16.8	29			
		(3 hrs. 50 min.)	51	6.7	6.1	20.7	50			
266	Male	B.S.	57	5.2	4.0	4.9	40	10%	5.7 hrs.	Terminal blood ammonia N. was: 243 ugm. %. Liver was dark and congestive on post., and 100 c.c. of bloody fluid were present in the abdomen
	23.0	B.I.	60.5	5.6	4.5		30	D/W		
		B.R.	60.5	3.8	2.9	3.3	27			
		15 min.	61	5.4	4.2		31			
		1 hr.	61	5.3	4.2	3.8	33			
		2 hrs.	65	3.5	2.9	6.2	37			
		4 hrs.	66	3.9	3.2	12.8	45			

B.S., Immediately before surgery. B.I., Just before ischemia.
B.R., Just before release of the ligatures. 15 min., 1, 2, and 4 hrs., Time after release.
10% D/W, Dextrose 10 per cent in water.

a slight degree of fibrosis and a patent shunt. In the survivor from the control group, no gross pathologic condition was found, and the latex rubber injection in the aorta did not reveal arterial anomalies.

DISCUSSION

The survival time of the hepatectomized dog and the permanently ligated liver ischemia dog, when maintained with intravenous glucose, is in most instances longer than 24 hours and death is in "hepatic coma." It has been shown that if the ischemia is maintained for only 1 hour, the survival time of normothermic animals is much shorter, the average being 5.5 hours, and death ensues in a shock-like state. It has been reported in the later cases that the mortality rate is close to 100 per cent—in spite of antibiotic protection. The present study indicates that tolerance to ischemia can be increased if the dogs are treated with ACTH.

Experimental and clinical evidence has demonstrated the important role that the liver plays in hemorrhagic and traumatic shock. In an ingenious experiment in dogs subjected to prolonged hemorrhagic shock, Frank, Seligman, and Fine (10) demonstrated that the liver protected the organism

TABLE II.—BLOOD CHANGES IN THE ACTH GROUP

Dog No.	Sex, Weight, kgm. Rose bengal	Blood sample	Hematocrit	Total acid soluble phosphorus mgm. per cent	Inorganic phosphorus mgm. per cent	Alkaline phosphatase Bod. units per cent	Nonprotein nitrogen mgm. per cent	Plasma pentose mgm. per cent	Blood glucose mgm. per cent	Intravenous infusion	Survival time
290	Male	B.S.	63	4.5	3.3	1.4	26	7.8	125	10% D/W	10 hrs.
	27.0	B.I.	64.5	5.3	4.0			21.0	278		
		B.R.	63	6.0	3.9			37.4	340		
	80	1 hr.	57	7.8	5.6	1.8	48	37.2	530		
		2 hrs.	65		6.5	1.5	31	22.0	350		
		4 hrs.	68	5.4	5.4	2.2	34	14.6	200		
Comments: Hemorrhage after release. Clotting time: 2.5 minutes at 2 and 3 hours after ischemia. On post.: 300 c.c. of bloody fluid.											
254	Female	B.S.	47.5	4.7	3.5	1.9	20	5.1	110	Saline	Indef.
	18.0	B.I.	45	7.3	5.7	1.5	16	9.6	189		
		B.R.	45	7.8	4.8	2.4	20	11.9	220		
	119	15 min.	45	6.0	5.3		23	14.7	260		
		1 hr.	45	5.5	4.5	2.8	24	9.1	186		
		2 hrs.	50.5	8.3	3.3	3.0	22	7.2	123		
		3 hrs.	45	8.4	5.0	1.2	20	6.3	96		
Comments: Remarkable appetite. Lost 2 kgm. in 3 mos. Alkaline phosphatase normal but rose bengal always around 50. Sacrificed: 3 months. Shunt patent. Fatty liver. No fibrosis.											
273	Female	B.S.	55	4.0	3.0			4.4	100	Saline	11 hrs.
	23.0	B.I.	59	8.7	6.2			8.8	145		
		B.R.	57	11.2	6.4			3.2	80		
	94	30 min.		11.2	7.6			3.7	70		
		1 hr.	58	9.6	7.1			4.2	70		
		2 hrs.	59.5	8.4	6.1			3.7	58		
		4 hrs.	59.5	7.4	5.8			4.0	60		
Comments: On post.: right lobes very pale and left lobes engorged and dark; 50 c.c. of bloody fluid in abdomen.											
222	Female	B.S.	61.5	5.0	4.8			7.7	170	Saline	6.5 hrs.
	26.0	B.I.	63.5	8.3	7.3			14.1	175		
		B.R.	63.5	7.2	6.6			7.0	137		
		1 hr.	57	9.4	7.5			12.0	161		
		2 hrs.	61	7.1	5.9			8.4	108		
		4 hrs.	62.5	6.8	5.7			5.9	62		
Comments: 80–100 c.c. of bloody fluid in abdomen. Shunt patent. Right lobes of the liver darker than left.											
314	Female	B.S.	42	5.1	4.0		22	9.9	210	Saline	Indef.
	21.4	B.I.	45	5.7	4.3		19	9.0	193		
		B.R.	46	5.2	3.8		19	10.8	202		
	128	15 min.	44.5	6.7	5.0		22	23.4	375		
		1 hr.	45	7.0	5.3		23	18.2	300		
		2 hrs.	45	4.6	3.4		22	10.6	184		
		4 hrs.	46.5	4.5	3.3		20				
Comments: Complete recovery. Rose bengal remained around 80 for 3 months. Sacrificed: liver appeared normal.											
322	Female	B.S.	51	5.0	3.9		21	23.0	265	Saline	2.5 days
	15.5	B.I.	49	4.5	3.4			16.5	200		
		B.R.	51.5	3.6	1.9			13.1	185		
	112	15 min.	53	4.2	2.9			20.5	287		
		1 hr.	46.5	4.2	3.0			13.3	208		
		2 hrs.	55.5	3.2	4.8			10.8	145		
		3 hrs.	56.5	5.7	4.3			12.5	96		
Comments: In first postoperative day: NPN 54, alk. phosphatase 7.6; inorg. phosph. 8.5; hematocrit 58.5; B. sugar 78; and pentose 13.4. On post.: shunt patent. Liver pale—scattered areas of necrosis in left lobes.											
330	Male	B.S.	61		6.0	3.3			148	Saline	15 days
	26.3	B.I.	61.5		6.9				138		
		B.R.	57.5		4.0				126		
	107	15 min.			4.3				157		
		1 hr.	60		3.4				137		
		2 hrs.	60		1.9	2.7			101		
		4 hrs.	55.5		2.4				77		
Comments: Before ACTH, B. sugar 81. Very sick after surgery. Only water. A week after, NH_3. N 170 μgm. per cent. Peritonitis. Necrotic pancreatitis. Scattered areas of necrosis in the liver. Shunt patent.											

B.S., Immediately before surgery. B.I., Just before ischemia.
B.R., Just before release of the ligatures. 15 min., 1, 2, and 4 hours, Time after release.
10% D/W Dextrose 10 per cent in water.

TABLE III.—BLOOD SUGAR

	Control dog	*Average of 6 ACTH treated dogs*
B.S.	96	167
B.I.	123	173
B.R.	83	158
15 min.	180	269
1 hr.	139	177
2 hrs.	77	119
3 hrs.	—	96
4 hrs.	82	66

B.S., Just before surgery.
B.I., Just before ischemia.
B.R., Just before release.
15 min., 1, 2, and 4 hours, Time after release of the ischemia.
Before any ACTH was given, 1 dog had 81 mgm. per cent, and before surgery rose to 148 mgm. per 100 ml. of blood.

from developing "irreversibility" since an adequate blood flow through the liver was life-protecting while viviperfusion through the systemic veins was not. Cohn and Parsons, Wayne and associates, and Hay confirmed Frank's conclusions. Leger and his associates have reported good results in shock patients by improving the liver blood supply with transfusions in the splenic vein.

In the present experiment, following the release of the vessels, the liver became progressively engorged and dark in a very few minutes, and the blood pressure showed an abrupt fall that slowly returned to normal. A short time later, shock appeared in the dogs that had a survival time of 12 hours or less. In other cases of experimental shock, the following factors have been considered as to its genesis: liberation of a toxic substance or of a vasodepressor substance by the injured liver, decrease in effective circulating blood volume due to blood and fluid loss into the liver, trapping of blood in the portal circulation, and a bacterial factor.

That some sort of toxic substance was liberated by the injured liver when the vessels were released has been discussed in Cannon's work on traumatic shock. Shorr, Zweifach, Chambers and associates made a good deal of investigation in shock and isolated a vasodepressor substance (VDM) liberated by the anoxic liver that produced a reduction in the effective circulating volume by pooling blood in the portal system. Frank and associates (8) have had difficulty in reproducing these experimental findings. They observed no effect upon arterial blood pressure or survival when VDM was injected intravenously to hepatectomized-nephrectomized dogs in amounts sufficient to produce plasma concentrations considerable in excess of those observed in advanced hemorrhagic shock. Others have observed similar findings.

Blalock and Parsons and Phemister felt that the shock causing factor was the marked reduction in the effective circulating blood volume due to the local hemorrhage and fluid which was lost into the extravascular space of the traumatized tissue. Mylon and Winternitz demonstrated in cross circulation experiments that shock could develop without local loss of fluid. The portal pressure is known to be increased in shock and following the release of the ligatures in liver ischemic experiments. In those cases, the physiologic effects of portal stasis and of decreased effective systemic blood volume must be considered in addition to those of reduced hepatic blood supply. Dogs do not tolerate acute portal vein occlusion and die in about an hour. Death can be delayed, but not prevented, if the systemic blood volume is maintained by blood transfusions or by occluding the celiac vessels. Andersen has demonstrated that survival time in acute portal vein occlusion is longer when blood is shunted from the vena cava to the portal vein above the ligature, thus increasing blood and oxygen supply to the liver. In a recent study by State and Lichtenstein, the stagnation of blood in the damaged liver after an hour of ischemia markedly decreased the effective systemic blood volume and seemed to them to be the most significant factor in the etiology of shock.

When no antibiotics were given to dogs with hepatic artery ligation, death ensued and was attributed to bacteria growing in the liver. Spore-bearing anaerobic rods are present in the liver of normal dogs and they abound in the necrotic livers of dogs dying after hepatic artery ligation. In normal healthy dogs, there is continual seeding of the liver by bacteria that pass from the

gastrointestinal tract to that organ via the portal vein. Cultures of portal vein blood were reported to be positive in 60 per cent of apparently healthy dogs and gram positive cocci were isolated in 92 per cent of those cases. Bacteria, with the exception of clostridia, are destroyed by phagocytosis in the liver. Nelson and Noyes (22) stated that the hypoxia and capillary distention present in shock may jeopardize the barriers which normally confine those bacterial toxins to the intestine, and could result in a migration into the circulation, thereby initiating a vicious cycle with even greater dilatation and loss of integrity of the capillaries. An experiment by Grana, Mann, and Essex also pointed out the importance that the liver has in the development of shock. Lethal doses of ascaris extract and hydatid fluid produced little or no effect on the blood pressure when infused into hepatectomized dogs.

That penicillin prevented liver necrosis following ligation of the hepatic artery was demonstrated by Markowitz, Rappaport, and Scott and by Davis, Tanturi, and Tarkington. Tanturi and associates considered lecithinase, identified with the alphatoxin of Clostridium perfringens type A organisms to be the main lethal factor. Other antibiotics, mainly of the tetracycline group, have been reported equally effective. The studies of Schatten threw serious doubt as to the importance of clostridia in the death following hepatic artery ligation and suggested that the responsible organisms were gram positive cocci. He protected dogs who had their hepatic artery excised by sterilizing the intestinal tract with neomycin. Fine and co-workers (9) had previously reported reduced mortality rates in a standardized hemorrhagic shock experiment in dogs pretreated with oral neomycin, an antibiotic which has little effect on clostridia in vivo or in vitro. They concluded that intraintestinal bacteria, but not clostridia, are involved in the phenomenon. It has been reported by Edward and associates that antibacterial defenses in the dogs which are injured by shock may be protected, to a large measure, by precooling the animal.

ACTH has been found experimentally and clinically to be of some value in treating traumatic shock, although this concept awaits further studies. Kibbey, D'Amour, and Smith reported that ACTH increased the survival time by 54 per cent in experimental traumatic shock of intestinal origin, and resulted in a 53 per cent increase in the rate of oxygen consumption. The metabolic stimulation so reflected was thought to be the logical explanation for the increased mean survival time, inasmuch as ACTH failed to improve the general circulatory pattern of shock. Raffucci (25) reported that ACTH in combination with antibiotics decreased the mortality rate in hepatic ischemia which was produced by simultaneously clamping the portal vein, celiac axis, and superior mesenteric artery. He found pork ACTH to be of more value than the hormone extracted from sheep pituitaries.

The blood changes in the current, shock-producing experiment were those common in the response to injury in general, in that persistent increases were observed in hematocrit, phosphorus, alkaline phosphatase, nonprotein nitrogen, ammonia nitrogen, amino acid nitrogen, and transitory increases in blood glucose and plasma pentose levels. Decreases were noted in blood sugar and pentose values once the liver glycogen was depleted. Considering separately the dogs that died and those that survived, regardless of treatment, the same trend of variation was found.

A progressive increase was noted in the serum alkaline phosphatase of the controls with no change in those treated with ACTH. This drug has been reported to decrease the phosphatase activity.

The nonprotein nitrogen decreased during surgery before the ischemia and rose markedly after the release of the vessels. The survivors tended to have a lower level than those that died.

The biologic energy transformations during shock have been studied by McShan

and associates in the blood, and by Le Page (17, 18) in the tissues. They regard adenosinetriphosphate (ATP) as the energy source directly coupled to function. Its breakdown in the tissues during shock results in an increase in phosphate and pentose in the blood. They find that the correlation between survival and the speed of return toward normal, as well as the magnitude of the original rise, strongly suggests that the breakdown products of the energy reservoirs are closely related to the development of shock. During the hypotension the oxygen supply to the tissues is decreased, and the resynthesis of ATP becomes increasingly ineffective.

The increase in the inorganic phosphorus following the release of the vessels was more marked in the control group, in spite of the fact that most of them were receiving glucose infusions. Glucose has been shown to decrease the plasma inorganic phosphate. ACTH has been reported to depress the renal threshold for phosphorus.

As already shown by McShan and associates and confirmed by us, the total pentose determination according to the method of Mejbaum is interfered with by glucose, thus making it impossible to evaluate the data when the blood glucose levels were not determined simultaneously with the pentose.

The blood sugar showed the expected increase that is known to occur following stress, liver injury, and ACTH therapy, and then progressively decreased during the 4 hours following ischemia. It was demonstrated that glucose was of no importance in increasing the tolerance to ischemia.

The toxicity of ammonia has been demonstrated in animals and in humans. Blood ammonia levels have been found to be increased in Eck fistula and hepatectomized animals, in liver disease, in hepatic coma, and in shock states. In the normal animal the intestine and kidney contribute ammonia to the circulating blood, while the liver removes part of it for the synthesis of urea. Nelson and Seligson (23) studied animals in shock and found that the concentration of ammonia both in the portal vein and in the renal veins is increased and that the liver does not reduce the ammonia adequately. This increase in ammonia is known to be present in all types of shock and usually is proportional to the degree of severity of the shock. In the present experiment, dogs with blood ammonia levels many times normal usually died, but some others died in a few hours with levels of only 200 to 300 micrograms per 100 milliliters of blood. Higher values have been maintained by us (27) in dogs infused with ammonium salts and glycine with no casualties. However, these animals had normal liver function. It appears probable that ammonia alone was not responsible for the death in our study.

The lowest excretions for rose bengal in the survivors were usually obtained immediately after operation, and it is reasonable to suppose that the recent liver injury and the portacaval anastomosis were responsible for the loss of excretory function for the dye. The improvement that was noted in the following weeks probably came from liver regeneration and closure of the venous shunt by the absence of the pressure gradient.

An inverse relation was usually present between the dye clearance and the alkaline phosphatase, the latter remaining slightly elevated for a month.

CONCLUSIONS

In comparing the two groups of animals in the present study, it is apparent that only a limited number of the observations and chemical data show any marked differences. That the survival time was increased is quite obvious. All control animals except 1 died within 12 hours and two-thirds of the ACTH treated animals survived more than 36 hours. The only gross change observed during the the period of surgery was that, in most instances, the liver of the dogs treated with ACTH developed a brownish red to bright red color during the period of engorgement

that followed release of the vessels. The liver of the control animals uniformly became quite dark. In the immediate postoperative period it was difficult to correlate the findings with eventual survival times. The pulse rate, hematocrit readings, and blood pressure patterns, which might reflect the systemic circulation, were about the same in the two groups.

The chemical data were, for the most part, nonconclusive. The control animals showed a somewhat higher inorganic phosphorus, and a lower alkaline phosphatase and nonprotein nitrogen. The blood ammonia usually was quite high in the nonsurvivors but could not be related as to the controls and ACTH treated dogs. These findings are tendencies only in that the small number of animals involved renders them stastically insignificant.

From the negative viewpoint, certain findings can be pointed out. Temperature of the environment was unimportant in that both the operating room and the animal quarters were air-conditioned. The sex and age of the animal evidently made little difference as to survival, as did the infusion of glucose.

An attempt was made to correlate some of the current concepts in the etiology of shock to compare them with our findings. In our previous study, we demonstrated that some blood passes through the liver during ischemia. This might tend to minimize the development of a toxic metabolite or a vasodepressor substance. The local loss of blood and periportal lymphatic fluid into the peritoneal cavity in a few instances could have led to circulatory failure. In most cases this was minimal and was not related to the use of ACTH. Circulatory failure due to pooling of the blood in the portal system was minimized in our study because of the patent portacaval shunt.

In spite of the chemotherapy used, the effect of shock resulting from infection and bacteremia is possible. However, the development of a deep shock in a short time makes this possibility remote. Interstitial hemorrhage due to damage of the liver capillaries, along with some fluid loss, could interfere with the energy supply to the already damaged liver cells and disrupt the ATP formation. The availability of usable plasma pentose determinations might have shed some light in this regard.

It is likely that the original drop in blood pressure following the release of the vessels is due to the rapid filling of the ischemic liver with blood. Two control dogs did not recover from this insult, even though the pressure in most instances began to resume its previous level within 4 minutes. One of the effects of ACTH is to increase the responsiveness of the circulatory system to l-norepinephrine, which might account for the survival differences. Another effect of ACTH is to increase oxygen consumption in the tissues. This could account for the color differences noted in the liver and may have been a factor in preserving the functioning liver cells in the treated animals.

SUMMARY

In dogs, ACTH has been found of value in increasing the tolerance to the shock-like state that follows the release of the ligatures after an hour of liver ischemia.

Of 13 control dogs whose afferent hepatic blood supply was ligated for 1 hour, only 1 survived and the others died in shock within the first 12 hours. Of 15 ACTH treated animals, 10 survived more than 36 hours—6 of them indefinitely—and only 5 died in shock within the first 12 hours following the release of the vessels. All animals received penicillin. Blood was drawn at periodic intervals and certain biochemical changes were compared in the two groups. Increase in serum alkaline phosphatase and nonprotein nitrogen frequently correlated with survival time. Glucose infusion failed to increase the tolerance to ischemia in that 3 out of 6 dogs which survived indefinitely did not receive glucose at all. Death was apparently caused by shock and not by hepatic coma and its possible genesis is briefly outlined. Only 1 of the dogs which survived indefinitely had an abnormal liver at the

time of sacrifice 3 months later, and that dog had a patent portacaval shunt.

ACTH evidently afforded some protection against shock in this experiment and might be of some value when ischemic fields are necessary in the surgery of liver tumors.

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AN EVALUATION OF PORTACAVAL SHUNTS FOR PORTAL HYPERTENSION

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WHIPPLE AND HIS ASSOCIATES established the fact that portal hypertension can occur in man when free flow of blood out of the portal venous system is obstructed either within the liver by cirrhosis or other diseases or outside the liver by disease of the portal vein and its tributaries. Splenomegaly and the development of collateral venous channels including esophageal varices are sequels of portal obstruction. Portal decompression by some form of portacaval anastomosis seemed a natural solution to the problem of bleeding from esophageal varices. As experience of many surgeons accumulated, it became apparent that small shunts between minor veins of the two systems were regularly ineffective and that anastomoses between the portal vein and vena cava or between the end of the splenic vein and the side of the left renal vein offered most promise. Reports of Blakemore (3), Linton (18), Rousselot, Child, and Jahnke, to name a few, have consistently supported the view that shunts made between the portal and caval systems are effective in controlling bleeding from esophageal varices. Others, such as Taylor (28), Cohn (6), Bennett and associates, and Ripstein, have doubted their value.

We join those who consider these operations useful in the management of selected patients who bleed from esophageal varices, and we wish to present our experience with 55 patients on whom splenorenal or direct portacaval shunts were performed from 1951 to 1955. Forty-seven patients had intrahepatic portal obstruction; 8 had extrahepatic portal obstruction and had not undergone splenectomy previously. The two groups will be described separately.

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PORTACAVAL SHUNTS FOR INTRAHEPATIC PORTAL OBSTRUCTION

Forty-three of the 47 patients, 25 males and 18 females, had some type of cirrhosis (Table I). Ages ranged from 5 to 73 years.

In 1 case sarcoidosis involved the liver. In 3 cases roentgenologic evidence did not indicate extrahepatic portal obstruction; hepatic function as judged by the usual tests of liver function was normal, and livers felt firmer than is normal but did not fulfill gross or histologic criteria for cirrhosis. These have been classified as instances of intrahepatic portal obstruction of undetermined etiology. The pathologist's reports of biopsies of the livers stressed increased fibrous tissue and venous spaces in periportal tissues.

Forty-four of the 47 patients had experienced hematemesis. In 2 of the 3 who had not bled esophageal varices were demonstrated by means of esophagograms. Acceptable evidence for a diagnosis of esophageal varices includes the positive evidence in the esophagogram or on esophagoscopic examination, or a history that bleeding was promptly stopped by esophageal tamponade. Esophagograms gave evidence of varices in 32 (69.5 per cent) of the 46 patients who underwent this test. In 11 of the 46 patients, other means of diagnosis indicated varices. In 3 patients, esophagoscopy was not done and diagnosis of esophageal varices remains presumptive (Table II).

Hospital mortality rate. Of the 47 operations 29 consisted of direct portacaval shunts be-

TABLE I.—SHUNTS BETWEEN THE PORTAL AND CAVAL VENOUS SYSTEMS FOR INTRAHEPATIC PORTAL OBSTRUCTION: 1951–1955

Cause of portal obstruction	*Patients*	*Males*	*Females*	*Age at operation, yrs.*
Cirrhosis				
History of alcoholism	17	14	3	39–64
History of hepatitis	7	3	4	5–54
Etiology indeterminate	16	6	10	25–73
Wilson's disease	2	1	1	21–28
Hemochromatosis	1	1	0	46
Subtotal	43	25	18	5–73
No cirrhosis				
Sarcoidosis	1	0	1	33
Etiology undetermined	3	2	1	22–55
Subtotal	4	2	2	22–55
Total	47	27	20	5–73

tween the portal vein and vena cava. One side-to-side anastomosis was made; the others were end-to-side. Six of the 29 patients died in the hospital, a hospital mortality rate of 20.7 per cent. One of these died 99 days after operation, having been unable to leave the hospital because of muscular inco-ordination and disability associated with Wilson's disease. Splenectomy with end-to-side splenorenal anastomosis was performed on the remaining 18 patients. One patient died, giving a hospital mortality rate of 5.6 per cent. Thus, 7 (14.9 per cent) of the 47 patients failed to survive operation.

Correlation between hospital mortality rate and preoperative hepatic function. Hepatic insufficiency is the commonest cause of death in the immediate postoperative period after portacaval or splenorenal anastomosis on patients with cirrhosis of the liver. The mortality rate then is greatly influenced by the selection of patients for operation. Data presented in Table III relate the operative mortality in our series of cases to results of tests of liver function most commonly performed preoperatively. The number of patients in some of the categories is small. For example, the prothrombin time of only 2 patients failed to come within 4 seconds of normal after administration of vitamin K. The fact that both survived the operation whereas 7 of 44 patients whose prothrombin time more nearly approached normal did not survive gives an incorrect picture of the importance of this factor. In general, the more impairment of hepatic function indicated by the individual tests, the greater was the postoperative mortality rate. With regard to retention of sulfobromophthalein (bromsulphalein), no significant change in mortality rate occurred until more than 23 per cent of the dye was retained after 1 hour. The mortality rate was greater when total serum albumin was low than when it was 3.6 grams or more per 100 cubic centimeters. In our patients, the cephalin-cholesterol flocculation test was not helpful in predicting the mortality rate to follow surgery; in other series like that of Ebeling and associates, the reverse has been true.

TABLE II.—EVIDENCE FOR DIAGNOSIS OF ESOPHAGEAL VARICES IN 47 PATIENTS WITH INTRAHEPATIC PORTAL OBSTRUCTION

	Patients
Esophagogram (46 patients)	
Positive	32
Negative	
Esophagoscopy positive	7
Diagnosis presumptive	3
Bleeding stopped by esophageal tamponade	4
Bleeding stopped by esophageal tamponade; esophagram not made	1
Total	47

Pressure in portal system. In 40 patients who had bled, portal pressure was measured after direct venipuncture at the time of laparotomy. In most instances the splenic or portal vein was used; in a few instances early in our experience, veins in the gastroepiploic system were used. The zero point was corrected as nearly as possible to the level of the portal vein. Only 5 of the 40 patients had portal pressures of less than 30 centimeters of saline solution. Twenty-eight had

TABLE III.—RELATIONSHIP BETWEEN HEPATIC FUNCTION AND HOSPITAL MORTALITY RATE IN PATIENTS WITH HEPATIC DISEASE

Test of hepatic function		*Patients*	*Hospital deaths*	
			No.	*Per cent*
Sulfobromophthalein retained after 1 hour, per cent	0–11	19	2	10.5
	12–23	18	2	11.1
	24–39	8	2	25.0
	>40	1	0	—
Total serum bilirubin, mgm. per 100 ml.	<1.0	15	1	6.7
	1.0–3.0	30	5	16.7
	>3.0	2	1	—
Serum albumin, gm. per 100 ml.	>4.0	19	3	15.8
	3.6–3.9	17	2	11.8
	3.0–3.5	9	2	22.2
Cephalin-cholesterol flocculation, grade	0–2+	23	3	13.0
	3+–4+	14	2	14.3
Prothrombin time, seconds above normal after administration of vitamin K	0–4	44	7	15.9
	>4	2	0	—

portal pressures between 30 and 49 centimeters and 7 had pressures greater than 49 centimeters of saline solution.

Portal pressures were measured in 18 patients before and immediately after anastomosis between the portal vein and vena cava and in 8 patients before and after splenorenal shunt. Reductions in pressure after establishment of direct portacaval shunts ranged from the questionable value of 0 in 1 patient to 36 centimeters of saline solution with a mean of 20 centimeters; after splenorenal shunt, from 2 to 13 with a mean of 6 centimeters (Table IV). Though data with regard to splenorenal shunts are scanty, the comparison supports the idea that direct portacaval shunts usually reduce the portal pressure to a greater degree than do splenorenal shunts.

The effects of portacaval and splenorenal shunts on bleeding from esophageal varices. Of the 17 patients who survived splenorenal shunt, 4 (23.5 per cent) bled subsequently. One of these had 3 small hemorrhages during the first year after operation but did not require blood transfusion. One had 2 severe hemorrhages 1 and 2 years after operation and a minor hemorrhage 2½ years after operation. The third had a hemorrhage of moderate severity 27 months after operation; the fourth a similar episode 22 months after operation.

Of the 23 patients who survived end-to-side portacaval shunt, 5 (21.7 per cent) bled subsequently. In 2 of these, all evidence, clinical in 1 and postmortem in the other, supported the idea that the bleeding came from a coexisting duodenal ulcer. In 1 other patient, the single episode of bleeding was minor. In the fourth patient, a terminal hemorrhage followed 6 months of increasing hepatic decompensation and was found at necropsy to have come from a varicose vein in the duodenum. In the fifth, bleeding was found at operation elsewhere to have come from a gastric varix.

Considering all patients as a group, 9 of 40 patients who survived shunting operations bled subsequently, an incidence of 22.5 per cent. Two of these died during or soon after the bleeding.

The 47 patients experienced a total of 75 hemorrhages during the 12 months before

TABLE IV.—EFFECTS OF DIRECT PORTACAVAL AND OF SPLENORENAL SHUNTS ON PORTAL PRESSURE MEASURED AT THE TIME OF OPERATION

	Portal venous pressure, cm. of saline solution			
	*Direct portacaval shunt**		*End-to-side splenorenal shunt*	
	Before	*After*	*Before*	*After*
Mean	42	22	36	30
Range	28–57	9–42	25–52	17–50
Difference	—	—20	—	—6

*Seventeen end-to-side and 1 side-to-side shunt.

anastomoses were made and the surviving patients had only 4 hemorrhages during the 12 months following the operations.

Survival rates after portacaval shunts for intrahepatic portal obstruction. Thirty-nine patients who survived operation were followed as of January 1, 1956. There were no deaths during the first year after operation. Of 23 patients eligible for a 2 year survival, 22 were alive, a 2 year survival rate of 95.7 per cent. Fifteen of 17 potential survivors (88.2 per cent) lived 3 years and 7 of 9 potential survivors (77.8 per cent) lived 4 years.

Effects of portacaval shunts on hepatic function of patients with cirrhosis. In the natural course of cirrhosis, the number and severity of the symptoms and signs may increase rapidly or slowly, or they may change little for many years, and sometimes the patient may improve with medical treatment. Knowing this, one might predict that it would be difficult to assess the effect of portacaval shunts on hepatic function in these patients unless such effects were great enough and consistent enough to be obvious. Transient depression of hepatic function frequently occurs immediately after these operations and is shown by increase in concentration of bilirubin in serum and prothrombin time, decrease in concentration of serum albumin, and so forth. Patients who fail to survive these operations commonly die from hepatic insufficiency. Any of these phenomena may follow other operations of comparable magnitude performed on patients with cirrhosis. There is no way to determine the relative importance of the portacaval shunt and of the general operative trauma, anesthesia, and so forth in the etiology of these acute changes in hepatic function.

Prolonged changes in hepatic function after direct portacaval or splenorenal shunt can be evaluated objectively by comparing results of common tests of hepatic function before and after operation.

Data were available concerning liver function tests performed before and from 5 to 42 months after 15 end-to-side portacaval and 10 splenorenal shunts (Table V). With regard to degree of jaundice, retention of sulfobromophthalein, concentration of albumin in serum, and prothrombin time, only a few improved, some grew worse, and the greatest number remained essentially unchanged during the period of observation. For example, serum bilirubin decreased by more than 0.5 milligram per 100 milliliters in 2 patients, increased by more than 0.5 milligram per 100 milliliters in 8 patients, and remained within 0.5 milligram per 100 milliliters of the value obtained preoperatively in 13 patients. Twenty-one of 23 patients maintained the concentration of protein in serum at 6 grams or more per 100 milliliters, and 22 of 23 patients maintained serum albumin concentration of 3 grams or more per 100 milliliters.

Clinical appraisal of the patients was similar: A few appeared worse, a few appeared improved, and the majority remained about the same. Chronic ascites had not developed in any case at time of follow-up.

A priori, one would expect that deviation of part or all of the portal blood from the liver would cause hepatic function to worsen if any significant amount of portal blood had been passing through the liver before the shunt was created. In our experience, which permits a follow-up of only 5 years, the changes in liver function have been less than we expected and except in a few patients to be described in whom neurologic symptoms developed, they have approximated those which might occur in the natural course of cirrhosis. When patients are selected for portacaval shunting on the criteria suggested by Linton (16), which we used to guide us, the operation seldom is followed by pronounced permanent depression of hepatic function.

NEUROLOGIC SYMPTOMS FOLLOWING PORTACAVAL ANASTOMOSIS

It has long been known that performance of an end-to-side portacaval shunting operation (Eck fistula) in dogs is often followed by episodic stupor, convulsions, apparent blindness, and sometimes death. Noting

that such symptoms appeared to be made worse when the animals were fed meat, physiologists have called the phenomenon "meat intoxication." McDermott and his associates (19) observed behavior reminiscent of this syndrome in a patient whose liver had been normal but in whom an Eck fistula had been constructed in the course of partial pancreatectomy. Periodic or chronic mental confusion, stupor, and gross tremors sometimes develop in patients with cirrhosis of the liver who have had no operations. These have been described by McDermott (20) and Sherlock and their associates. These investigators, as well as Havens and Child and Hurwitz and Allison also have described similar neurologic symptoms in patients with cirrhosis who have portacaval shunts. In some, the appearance of symptoms within a few weeks after operation strongly suggests that the operation was the precipitating factor; in others, a delay of a year or more before symptoms became manifest makes the relative importance of the operation and the hepatic disease difficult to evaluate.

Neurologic symptoms did not develop after splenorenal anastomosis in any of our 17 patients, but neurologic symptoms of varying severity did develop subsequently in 6 of our 23 patients who survived end-to-side portacaval anastomosis. None of the 6 had any recognizable neurologic symptoms before operation. In 3 the problem was persistent; in 3, transitory. Brief summaries of these patients' histories follow:

CASE 1. A man, aged 46 years, had severe alcoholic cirrhosis and a duodenal ulcer from which he had bled 16 years previously. A modest memory deficit was noted preoperatively. Two weeks following end-to-side portacaval shunt, a fine tremor of the hands developed with superimposed irregular jerking movements, occasional ataxia, mental confusion, increased impairment of memory, and apraxia. These symptoms continued for 1 year. A diet then was prescribed which supplied only 40 grams of protein daily and the mental symptoms and tremor cleared remarkably. Symptoms of exacerbation of the duodenal ulcer appeared subsequently and were treated in the usual manner. A gastrointestinal hemorrhage occurred and was followed by hepatic failure and death. Necropsy showed a patent portacaval shunt, no evidence for esophageal varices, and a duodenal ulcer which appeared to be the source of the bleeding.

TABLE V.—EFFECTS OF DIRECT PORTACAVAL AND SPLENORENAL SHUNTS FOR INTRAHEPATIC PORTAL OBSTRUCTION ON CERTAIN TESTS OF HEPATIC FUNCTION 5 TO 42 MONTHS AFTER OPERATION

Test and variation in result	*Patients with end-to-side shunts*		
	Portacaval	*Splenorenal*	*Total*
Total serum bilirubin, mg. per 100 ml.			
Increased >0.5	8	0	8
Remained within ±0.5	7	6	13
Decreased >0.5	0	2	2
Sulfobromophthalein retained after 1 hour, percentage points			
Increased >5	7	4	11
Remained within ±5	6	6	12
Decreased >5	1	0	1
Serum protein, gm. per 100 ml.			
Remained >6	13	8	21
Less than 6	2	0	2
Serum albumin, gm. per 100 ml.			
Remained >3.0	15	7	22
Decreased >0.4	4	3	7
Remained within ±0.4	8	4	12
Increased >0.4	3	1	4
Prothrombin time, seconds (after K)			
Increased >2	3	0	3
Remained within ±2	10	4	14
Decreased >2	0	2	2

CASE 2. A woman, 55 years of age, had cirrhosis which was probably the result of an episode of hepatitis 10 years previously. She had experienced one massive hemorrhage from esophageal varices. An end-to-side portacaval anastomosis was made. Six weeks later coarse tremor of the hands and slurred speech developed. Two weeks following this the patient experienced visual and auditory hallucinations and became semicomatose. These symptoms cleared up but recurred in less severe form for from 1 to 2 days during the subsequent 8 months; at the end of that time a second episode of near coma occurred.

The patient was evaluated again 1 year after operation. Neurologic examination provided no evidence for a localized lesion in the brain. Neurologic symptoms continued, and the patient spent 5 months in a neuropsychiatric hospital because of them. A diet low in protein was recommended but we were unable to determine the degree to which it was followed because the patient was no longer under our care. Tests of liver function showed little change as compared with those obtained preoperatively (Table VI).

The patient died 26 months after operation as a result of cerebral injuries sustained in a fall.

CASE 3. A man, 47 years of age, who had cirrhosis gave a history of alcoholism and of having had hematemesis and melena on 2 occasions during the year prior to admission to the clinic. End-to-side portacaval anastomosis was performed. Three weeks after operation he was readmitted to the hospital because of anorexia and weakness. Depression, somnolence, and mental confusion appeared, became more intense, and culminated after 2 weeks in an episode of coma difficult to distinguish from that of hepatic insufficiency. Two days later the patient became responsive again. A diet containing only 40 grams of protein daily was used. Gradual improvement occurred until the patient appeared asymptomatic and was dismissed 2 weeks later. Six months later, it was learned from the patient's home physician in another country that episodes of coma and mental confusion, drowsiness, amnesia, slurring of speech, and tremor of the hands have continued. We are unable to determine whether the diet low in protein has been continued.

CASE 4. A woman, 25 years of age, had cirrhosis which followed hepatitis. She had undergone splenectomy 8 years previously because of 2 episodes of bleeding from esophageal varices. Several episodes of bleeding followed in the next 8 years and culminated in a massive hemorrhage. An end-to-side portacaval shunt was made. Five months later 2 transitory episodes of alteration of consciousness which were in many ways similar to those seen in petit mal occurred on a single day. Tremors and ataxia were absent. The patient was re-evaluated 8 months after operation, at which time she looked well. Neurologic examination was negative and an electroencephalogram disclosed no specific abnormalities. Hepatocellular function, as judged by liver function tests, had deteriorated slightly (Table VI).

Twelve months following the first attack the patient had a second episode of altered consciousness which again resembled petit mal; during this episode she drove her car off the road and through a fence. Consciousness returned a few minutes thereafter. There is no record of any convulsion having been present but the patient was alone at the time. More recently there has been deterioration of this patient's hepatic function without further evidence of neurologic symptoms.

CASE 5. A man, aged 43 years, had cirrhosis for which no certainly etiologic factors could be obtained. A moderate degree of ascites and swelling of the ankles developed 6 months preoperatively and was followed by bleeding from esophageal varices. The ascites responded to medical management. An end-to-side portacaval shunt was made. The patient's general condition remained unchanged in that easy fatigability and slight edema of the ankles persisted. Ascites was not demonstrable clinically. One year after operation neurologic symptoms appeared for 2 days. These consisted of jerking ataxic movements and a feeling described as great nervousness. There was no coma. This isolated episode was not repeated during the following 2 years and because of this a diet low in protein has not been prescribed. Tests show considerable impairment of liver function (Table VI).

CASE 6. A girl, aged 15 years, had experienced several episodes of jaundice beginning at the age of 11 and was considered to have postnecrotic cirrhosis of the liver. An episode of hematemesis and melena occurred and the value for hemoglobin was 5 grams per 100 milliliters of blood. An end-to-side portacaval shunt was established. The patient recovered promptly from the operation. Four weeks later she became listless, had a coarse tremor of the hands, was mentally confused, and did not speak clearly. These symptoms persisted for 3 days, then disappeared. They have not recurred during the ensuing 18 months, although no attention has been paid to limiting the intake of protein.

Portal thrombosis following portacaval anastomosis. Widespread thrombosis in the portal venous system can develop after operation and was the primary cause of death in the single patient in the present series who died after splenorenal anastomosis. Summary of another case is illuminating in this regard:

CASE 7. The patient was a man, 22 years of age. Intrahepatic portal obstruction was diagnosed from the portal venographic study, but results of liver function tests were normal and gross inspection and biopsy of the organ at the time of laparotomy did not disclose cirrhosis. Splenectomy and splenorenal anastomosis were performed because of portal hypertension, congestive splenomegaly, and bleeding from esophageal varices. Ten days after operation progressive anorexia and pain in the lumbar region followed by diarrhea developed. The pain in the back became excruciating. An excretory urogram disclosed normal renal function bilaterally from which it was assumed that if portal thrombosis were present it had not come to occlude the renal vein via the shunt. Exploratory laparotomy was performed on the nineteenth day after operation and 1,500 cubic centimeters of ascitic fluid was removed from the abdomen. The upper two-thirds of the small intestine appeared edematous and dusky but was viable; the lower third appeared normal. A diagnosis of thrombosing process in the portal venous system was made, the abdomen was closed, and the patient was given 50 milligrams of heparin intravenously every 4 hours. A splanchnic block was performed for relief of pain. Improvement was dramatic. Pain disappeared and appetite returned. Administration of heparin was discontinued after 5 days and the patient recovered.

The diagnosis of acute and progressive thrombosis in part of the portal system is difficult to make with certainty during life.

TABLE VI.—RESULTS OF TESTS OF LIVER FUNCTION IN CASES 2, 4, AND 5

	Case 2		Case 4		Case 5		
						After operation	
Test	Before operation	1 yr. after operation	Before operation	8 mos. after operation	Before operation	11 mos	2 yrs.
Serum bilirubin, mgm. per 100 ml.							
Direct	0	0	0	0	0	0	0
Indirect	0.5	1.16	1.5	2.1	1.4	2.7	2.1
Sulfobromophthalein retained after 1 hr., per cent	10	14	8	18	16	36	26
Prothrombin time, seconds	19	22	19	20	24	21	23
Serum protein, gm. per 100 ml.	7.1	6.5	6.1	5.8	6.1	6.0	5.6
Albumin	3.9	3.7	3.8	3.4	3.7	3.0	3.2
Globulin	3.2	2.8	2.3	2.4	2.4	3.0	2.4
Hemoglobin, gm. per 100 ml.	10.5	14.1	—	—	12.6	12.2	12.7
Cephalin-cholesterol flocculation, grade	—	—	1+	0	4+	—	2+

The operative finding together with the response to heparin seemed to establish it in this case. We have suspected this condition on clinical grounds alone following the shunting operations in 3 more patients, have treated them with heparin, and have seen remarkable improvement within 48 hours in 1, significant improvement in a second, and an equivocal response in a third.

As a result of these experiences we stand ready to administer heparin after venous shunting operations to patients who have persistent anorexia, abdominal pain which can be vague or severe, slight distention of the abdomen, and sometimes fever. If the symptom complex is due to incipient portal thrombosis, we believe the process may be arrested by this medication.

PORTACAVAL SHUNTS FOR EXTRAHEPATIC PORTAL OBSTRUCTION

When obstruction exists in the extrahepatic part of the portal system, it usually involves the portal vein itself and sometimes the splenic vein as well. Isolated thrombosis of the splenic vein has been reported and we have encountered 1 such patient since the present series was studied. Development of techniques for portal venography has rendered diagnosis more accurate than it was in the past.

Between 1951 and 1955, we encountered 13 patients with extrahepatic portal obstruction whose spleens had not been removed previously. Six of these were small children from 2 to 6 years of age, 1 was a larger child 12 years of age, and the remainder were adults.

Three of the adults were found to have thrombosis of the splenic vein which precluded splenorenal anastomosis and in these splenectomy alone was performed. One of these has bled several times since operation, 1 had no further bleeding and died from coronary occlusion 1 year later, and 1 has not bled in the 4 years since splenectomy.

Splenectomy with end-to-side splenorenal anastomosis was performed in 8 cases. Four of these operations were on children 4 to 6 years of age in whom the splenic veins measured approximately 5 millimeters in diameter. All of these bled subsequently and all later underwent transesophageal ligation of varices. Four splenorenal shunts were established in patients whose splenic veins proved to be 1 centimeter or more in diameter; 1 of these had a single minor hemorrhage subsequently.

Because of the poor results following splenorenal shunting in small children in whom the anastomoses were necessarily tiny and probably became thrombosed, 2 children whose symptoms were severe enough so that we felt obliged to intervene were subjected to splenectomy alone. Both have bled subsequently on many occasions.

There were no postoperative deaths in the 13 cases.

COMMENT

Hospital mortality. The hospital mortality rate after direct portacaval anastomosis in our series was 20.7 per cent; after splenorenal shunts, 5.6 per cent. Without interpretation, these figures suggest that splenorenal shunt carried a much lower mortality rate than portacaval shunt. Linton (18) considered this to be the case; doubtless this opinion is a factor in his choice of splenorenal anastomosis as the procedure of choice for the majority of patients with cirrhosis for whom shunting is indicated. Blakemore (3) reported almost identical postoperative mortality rates for direct portacaval and splenorenal anastomoses in patients with cirrhosis of the liver. It is true that the liver is handled and traumatized more when a portacaval shunt is made than when a splenorenal shunt is made. Unless a splenorenal shunt were so effective that portal blood no longer entered the liver or that blood even flowed from the liver into the portal system, one would expect the total hepatic blood flow to be diminished more by an end-to-side portacaval shunt than by a splenorenal shunt. However, the operative mortality rate for patients with cirrhosis is also greatly influenced by the selection of patients for operation, as mortality is high among those whose hepatic function is greatly impaired. Study of our data has indicated that we have subjected more patients in whom the risk of operation was considered to be unusually high to portacaval than to splenorenal shunts. Though end-to-side portacaval shunts may be followed by a higher postoperative mortality rate than splenorenal shunts, we doubt that the difference is as great as our figures would indicate if considered without interpretation.

Our data indicated that postoperative mortality was increased when the retention of sulfobromophthalein after 1 hour exceeded 24 per cent, when the concentration of serum bilirubin was above normal and when the concentration of serum albumin was between 3.0 and 3.5 grams per 100 milliliters. Others, notably Linton (16) and Blakemore (3), have made similar comparisons in series of patients in whom the range of variance of these tests was wider and obtained more striking correlations. Because we took their data into account and followed Linton's criteria for selection of patients for operation, we operated on few patients who had as severe hepatic decompensation as some of Linton's and Blakemore's earlier patients had. Because the "spectrum" represented by our data is narrower than theirs, the differences in mortality rates when grouped according to results of preoperative hepatic function tests are less striking than those they observed. For example, their series contained several patients with chronic ascites and with values of serum albumin less than 3 grams per 100 milliliters. We operated on only 1 patient with chronic ascites and none with a serum albumin level of less than 3 grams per 100 milliliters.

Cirrhosis and survival. As a result of studies by Ratnoff and Patek, Douglass and Snell, Shull, and Nachlas and associates, it is commonly stated that from 50 to 80 per cent of patients with cirrhosis die within a year after the first hemorrhage from varices. These observations have comforted those who perform hazardous operations on cirrhotic patients in an effort to prevent bleeding. In all such series some patients do not die within a year after their first hemorrhage and continue to live for many years, perhaps having occasional episodes of bleeding. It is reasonable to infer that many of those who die with the first hemorrhage or soon after it have more seriously damaged livers than those who live despite bleeding. Patients who undergo portacaval shunting operations are highly selected so that those with liver disease so advanced that they would be unlikely to survive operation are excluded. As Child has so aptly pointed out, groups of unselected patients used to study the natural history of cirrhosis are not similar to groups

of patients with cirrhosis selected for portacaval shunting and cannot be used as a standard against which to measure the effectiveness of portacaval shunts in prolonging the life of the cirrhotic. Thus far, no data are available concerning the fate of patients who have cirrhosis, have bled, have hepatic function adequate to permit shunting, but have not undergone operation. Admitting that a final answer to the question of the effect of portal decompression on longevity in patients with cirrhosis is not at hand, we can say that it is probable that some of the patients operated on fall into the group which would have survived several years without operation and others fall into the group which otherwise would have died of hemorrhage. Since the future cannot be predicted accurately for a given patient who has bled from varices, we plan to continue advising portal decompression for those whose hepatic function is adjudged adequate so that they can withstand operation.

Effectiveness of portal decompression in prevention of bleeding. Several have questioned whether portal decompression can prevent bleeding from varices. Experience with several patients who have required as many as 50 blood transfusions during several months preceding operation and who have had no bleeding for 2 or 3 years after operation has convinced us that the procedure can be effective. Protection is not absolute, however. The history of 1 of our patients, who was subsequently operated on and whose case was reported by Cohn (7), demonstrates clearly that bleeding from varices can occur despite the presence of a functioning end-to-side portacaval shunt. Three years after the shunt was established because of bleeding from varices resulting from postnecrotic cirrhosis of the liver, massive hematemesis and melena developed. Cohn sutured a bleeding varix in the upper part of the stomach. He measured the portal pressure at the time and found it to be only 20 centimeters of water. The child died of hepatic failure 4 months later. Necropsy revealed that the shunt was patent.

Although Child has reported the enviable record of no bleeding among 48 patients for periods of 1 month to 4 years after direct portacaval anastomosis, most surgeons have recorded recurrence of bleeding in some of their patients. Linton (18) reported recurrent bleeding in 14.7 per cent of 60 patients after splenorenal shunts had been established and in 11 per cent of 18 patients after direct portacaval shunts. Blakemore (3) stated that 12.5 per cent of 32 patients bled after splenorenal anastomosis performed for intrahepatic portal obstruction whereas 6.6 per cent of 45 patients bled after direct portacaval anastomosis. Jahnke's figures were 20 per cent and 4.5 per cent respectively. In our series, 23.5 per cent of 17 patients with liver disease bled again after splenorenal anastomoses and 21.7 per cent of 23 patients had bleeding after portacaval anastomoses. In general, relatively minor hemorrhages have been commoner than massive bleeding. As Palmer and Brick have pointed out, bleeding in cirrhotic patients may arise from causes other than esophagogastric varices, and in 2 of our patients all evidence indicated it was from coexisting duodenal ulcer.

Like others, we found that the majority of patients who had bled from esophageal varices had portal pressures of 30 centimeters or more of water when measurements were made at the time of laparotomy. End-to-side portacaval anastomosis was followed by an immediate fall in portal pressure which averaged 20 centimeters of water. In our hands, splenorenal shunts have been less effective in reducing portal pressure, the average reduction in 8 patients being only 6 centimeters of water. Furthermore, it has been more difficult for us to obtain large well placed splenorenal anastomoses as consistently as direct portacaval anastomoses. When portal venography has demonstrated that the portal vein is not thrombosed, that vein is usually large and sturdy. Splenic veins, however, vary considerably in size, typically have fragile walls, and may be difficult to dissect from the tail of the pancreas. In our experience, direct portacaval anas-

tomosis is easier than splenorenal anastomosis to perform. As one of us (G. A. H., 10) has stated elsewhere, these considerations led us to regard the end-to-side portacaval anastomosis as the better procedure when it can be done.

Neurologic complications. The occurrence of serious neurologic complications in 3 (13 per cent) of 23 patients with end-to-side portacaval shunts, however, invited us to re-evaluate this position. Because these symptoms sometimes occur in patients with cirrhosis of the liver who have had no operations, it follows that they could appear also after splenorenal shunts. Indeed, 1 such case has been reported by McDermott, Adams, and Riddell. Still, the fact that neurologic symptoms did not develop in any of our patients with splenorenal shunts suggests that the syndrome is less likely to occur after splenorenal anastomosis than after establishment of an Eck fistula. The number of patients in both of our groups is much too small to permit us to generalize in this way or to make definitive statements concerning the incidence of the disorder after the operation establishing an Eck fistula.

Child, in a personal communication, estimated the incidence of neurologic symptoms in his large series of patients with end-to-side portacaval anastomosis as similar to ours. Blakemore (4) recalled transitory periods of dizziness with some twitching of the hands and fingers that developed after shunts had been established in only 4 of 186 patients with cirrhosis and added that these patients did not lose consciousness. Linton (17) stated that neurologic symptoms appeared in "relatively few" of more than 100 cases in which portacaval shunts had been established, and that these symptoms occurred more frequently after direct portacaval than splenorenal anastomosis. As others have pointed out, these neurologic symptoms can be minimized or sometimes abolished by use of a diet providing only 20 to 50 grams of protein daily.

If one accepts as a working hypothesis the idea that neurologic symptoms are more likely to occur after end-to-side portacaval than after splenorenal anastomosis, he must take this into account in determining the procedure to be done. Though we believe that a direct portacaval shunt provides better decompression of the portal system than does a splenorenal shunt, we have been sufficiently impressed with the control of bleeding after splenorenal shunt in many of our patients and especially in those of Linton that we are prepared to utilize this operation more than we did a year or so ago. Our incidence of recurrent bleeding after splenorenal shunt was too high to be acceptable, but study of these cases has indicated that bleeding occurred principally in cases in which anastomosis was not entirely satisfactory, usually because the splenic vein was too small. At present, we are estimating the size of the splenic vein with the aid of splenic portography and electing splenorenal anastomosis when the vein is large.

Extrahepatic obstruction. The surgical treatment for patients with extrahepatic portal obstruction, splenomegaly, and bleeding from esophageal varices is well established. Splenectomy as the sole procedure is followed by recurrence of bleeding in at least half the cases. Because the disease itself usually makes satisfactory direct portacaval anastomosis impossible and because splenectomy precludes subsequent splenorenal anastomosis, construction of a splenorenal shunt at the time of splenectomy, if at all possible, is of the greatest importance when extrahepatic portal obstruction is present. Addition of a venous shunt to the operation does not increase the risk when the liver is normal.

The diagnosis of extrahepatic portal obstruction is not always obvious at the time of laparotomy. The commonly held view that all such patients have grossly distended tortuous intra-abdominal veins is wrong. We have encountered patients who had been considered to have no portal hypertension at the time of previous operation, usually splenectomy, but who were proved to have extrahepatic portal obstruction with portal hypertension when a portal venogram was

made and portal pressures were measured. Furthermore, splenomegaly may be noted in some patients with extrahepatic portal obstruction before gross bleeding has occurred.

Splenectomy, performed for a condition such as splenic anemia, can be followed by bleeding from esophageal varices. If the surgeon is to take all steps possible to prevent postsplenectomy bleeding in such cases, he must appraise the portal system accurately with the aid of portal venography and measurement of portal pressure whenever he contemplates performing splenectomy unless the underlying disease clearly does not involve portal obstruction. It is our practice to obtain a splenic portogram after the patient has been anesthetized immediately before an incision is made. The technique of injecting from 25 to 50 milliliters of a radiopaque substance percutaneously into the spleen through the tenth intercostal space and of taking a plain roentgenogram as the last of the material is injected is simple and has been described by us (11) and many others. Atkinson and Sherlock have described a technique by which portal pressure is estimated by measuring intrasplenic pressure at the time the splenic portogram is made. These workers perform both procedures under local anesthesia. We have had no experience with this method but have measured portal pressure with a water manometer after the abdomen has been opened. The importance of adjusting the zero mark to the level of the portal vein has been justly emphasized by Taylor and Egbert.

For small children an exception to the general rule that splenectomy with splenorenal anastomosis is the treatment of choice for extrahepatic portal obstruction seems necessary. This belief is based on the observation that in children up to 6 years of age and perhaps even older, the splenic vein is usually small enough that splenorenal shunts are inadequate and tend to become thrombosed. Our poor results with 4 such children have been described. Transesophageal ligation of varices in 5 such children has produced remissions which are still in effect after 8 to 28 months. Our present plan for these small children is to obtain accurate diagnosis by splenic portography and to employ transesophageal ligation of varices as a primary procedure in the hope of obtaining a significant remission of symptoms. With the passage of the years and enlargement of the splenic vein, which one can legitimately expect to occur, an effective splenorenal shunt may be possible later.

Our experience with treatment of recurrent bleeding after splenectomy in cases of extrahepatic portal obstruction has been recorded elsewhere (12).

SUMMARY AND CONCLUSIONS

Our experience up to January 1, 1955, in the use of shunts between the portal and caval venous systems in the treatment of portal hypertension with bleeding from esophageal varices has consisted of 55 cases.

Forty-seven patients had intrahepatic portal obstruction caused in all but 4 instances by cirrhosis of the liver. Thus far, we have utilized these operations almost entirely for patients who have bled from varices and who have not had chronic intractable ascites. In selecting patients for operation we used criteria suggested by Linton and by Blakemore. The evidence indicates that although large well placed portacaval or splenorenal anastomoses do not provide absolute protection against subsequent gastrointestinal bleeding, they are effective in most instances. The effect of portacaval shunt on survival of patients with cirrhosis of the liver who have bled from esophageal varices cannot be assessed at present due to lack of suitable controls. Survival rates are greatly superior to those of unselected patients with cirrhosis who have bled, many of whom have impairment of hepatic function which is too great to permit operation. The serious neurologic symptoms which followed end-to-side portacaval anastomosis in 3 patients and the transient symptoms which occurred in 3 others in our series were described in some detail. Although the factor of chance may account for the greater incidence of neuro-

logic symptoms among our patients than that reported by others, our experience has prompted us to utilize splenectomy and splenorenal shunt when splenic portograms indicate that the splenic vein is large.

Thirteen patients were seen who had extrahepatic portal obstruction and who had not undergone splenectomy previously. In general, when the splenic vein is patent in these patients splenectomy with end-to-side splenorenal anastomosis is considered the operation of choice. Unsatisfactory results in 4 children, aged 4 to 6 years, have led us to consider them an exception to this rule. Splenic veins in small children with this disease are usually small. We have assumed that this is the reason splenorenal shunts failed to control bleeding in these children. At present we are performing transesophageal ligation of varices in these children, hoping to obtain remissions from bleeding for enough years so that the children can grow larger and become better subjects for splenorenal anastomosis.

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LONG TERM ANTICOAGULANT THERAPY

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THE MORTALITY, morbidity, and economic loss from thromboembolism stand foremost among medical problems today. The basic etiology of diseases characterized by thromboembolic events is little understood. Among the few therapeutic additions to the field since the turn of the century, anticoagulant drugs stand out in importance. Since their introduction they have been the center of great controversy, their effectiveness challenged by some authorities, their danger emphasized by others. The necessity for rigid control of their administration is recognized by both critic and champion, and it appears likely that the extremes of opinion may eventually be resolved about this point as increasing simplicity and accuracy of such control make them more universally available.

The fundamental principle of anticoagulant therapy is a cautious interference with the coagulation mechanism. Until recently the favorable effects were considered to be: (1) the prevention of the formation of a thrombus or (2) a limitation of its extension once it was formed. This second effect not only serves to prevent the development of new friable clot easily dislodged and broken off as embolic fragments, but also permits organization and fixation and resolution of existing thrombi. The recent important work of Wright and her associates demonstrates a third effect, namely, the recanalizing influence of at least one of the prothrombin depressants. These three influences then constitute the basic rationale for the use of anticoagulant drugs.

The active treatment with anticoagulants of patients with various thromboembolic conditions is employed in most hospitals. Because of the fear of hemorrhage many physicians hesitate to use them on an outpatient basis. Some conditions, however, require extended treatment, notably migratory thrombophlebitis and recurrent arterial embolism. Others, such as coronary artery disease and retinal vein thrombosis, have been reported to be favorably influenced by extended therapy.

The rationale of the long term use of anticoagulants in patients with coronary heart disease should be presented briefly. Atherosclerosis of the coronary vessels is still a disease of unknown origin, although there are many clews as to factors important in its etiology. There can be, therefore, no specific treatment to prevent the development of atherosclerotic changes in the coronary arterial wall. It is, however, significant that myocardial infarction as a complication of coronary disease is almost always—some say always—due to a thrombotic occlusion at the site of local plaque formation, that when mere narrowing of the coronary arterial tree takes place gradually without thrombotic occlusion there develops a compensatory collateral circulation allowing adequate myocardial oxygenation, and that in the experimental animal coronary and other atherosclerotic lesions may be produced but a thrombotic occlusion has never been seen to develop. It is therefore reasonable to try to modify the course of coronary disease in man by attempting with the use of anticoagulants to prevent thrombotic coronary arterial occlusions. Even though coronary atherosclerosis may proceed unchanged, actual myocardial infarction may theoretically be prevented and opportunity be provided for optimal growth of collateral channels.

It is the purpose of this article to report experience with 70 patients who received

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TABLE I.—DURATION OF TREATMENT

Mos. of treatment	*No. of cases*
6–12	17
13–18	8
19–24	11
25–30	7
31–36	5
37–48	7
49–60	6
61–72	2
73–84	4
85–96	2
108–120	1
Total	70

continuous therapy with anticoagulant drugs for periods varying from 6 months to more than 8 years and to offer comments on various phases of the experience.

SELECTION OF CASES

Of the 70 patients whose records have been included in this report, only those patients who have received a minimum of 6 months uninterrupted treatment with an anticoagulant drug are included. Likewise, only those patients are included whose prothrombin levels during the total period of treatment averaged less than 30 per cent, as determined by the two stage method. These criteria necessitated the exclusion of many patients who for a number of reasons were uncontrolled over extended periods of time. As will be emphasized later, such periods of "escape" are considered an important factor in the failure of anticoagulant therapy in many instances. The series in other respects is unselected, and included all patients receiving long term anticoagulant therapy whose prothrombin determinations were done in the coagulation laboratory of Presbyterian-St. Luke's Hospital, Chicago.

TABLE II.—DRUGS ADMINISTERED

Drugs administered	*No. of cases*
Dicumarol	20
Phenylindanedione	10
Dipaxin	9
Tromexan, dicumarol	6
Tromexan	5
Dicumarol, dipaxin	5
Dicumarol, phenylindanedione	4
Tromexan, dipaxin	4
Tromexan, dicumarol, dipaxin	3
Tromexan, phenylindanedione	1
Coumadin sodium, dipaxin	1
Tromexan, dicumarol, phenylindanedione	1
Sintrom	1

DURATION OF TREATMENT

The data regarding the duration of treatment are listed in Table I. It will be seen that 50 of the 70 patients have received anticoagulant drugs for over 1 year, and 21 for more than 3 years. The longest period is 9 years.

DRUGS AND DOSAGE

As indicated in Table II, several long-acting anticoagulant drugs have been employed in this series. In many instances, the first few days of anticoagulant therapy represented the combined effects of a short-acting preparation (heparin) and a long-acting drug. Once prothrombin levels had been satisfactorily depressed by the latter, heparin was discontinued. No patient received long term heparin treatment. As new anticoagulant compounds appeared, changes in the choice of drugs were frequently made in order to assess their efficacy by clinical trial. The preparations receiving the widest use were dicumarol, phenylindanedione, and dipaxin. In no case were two long-acting anticoagulants given simultaneously for long term control.

The dose of any anticoagulant drug employed in this series was an individual matter, entirely dependent on the response of the patient. For example, average daily doses of dicumarol ranged from 25 to 87.5 milligrams, of phenylindanedione from 25 to 125 milligrams, and of dipaxin from 2.5 to 7.5 milligrams.

TECHNIQUES OF ADMINISTRATION

The technique of administration is considered of the utmost importance in the effectiveness and safety of the drugs. The decision as to whether to use an oral prothrombin depressant alone or to use it in conjunction with heparin will depend on the type and character of the disease which is under treatment. When conditions require emergency control, heparin must be given since all prothrombin depressants are characterized by varying periods of delay in producing adequate therapeutic effects.

When heparin is indicated, it has been our practice to administer it intravenously since by this route (1) its effect is more promptly obtained, (2) its influence on the clotting mechanism can be more accurately controlled, (3) it is more rapidly excreted, and (4) although heparin interferes with the conversion of prothrombin to thrombin and definitely influences the prothrombin assay, when used intravenously in conjunction with the prothrombin depressants it does not interfere with their control, provided that blood drawn for the estimation of prothrombin depressant effect is taken a minimum of 6 hours following the last dose of heparin.

When the patient is first seen a blood sample is drawn for the prothrombin determination. At the same time, if heparin is to be given, a coagulation time is done and if normal, an initial 50 milligram dose of heparin is injected intravenously and 15 to 30 minutes later another coagulation time is taken. In general, a doubling of the control time at 15 to 30 minutes is sought and subsequent heparin doses are adjusted to achieve this effect. The adjusted dose is repeated every 4 hours until the prothrombin level has been reduced by oral drugs to between 20 and 30 per cent of normal.

As soon as the original prothrombin reading is known, the prothrombin depressant is started. The dose of this drug is guided by daily prothrombin levels until the therapeutic range is reached and determinations are gradually spaced at increasing intervals until they are performed every 2 weeks. The interval is usually not extended beyond this. It is true that the prothrombin levels of many patients will remain stabilized over periods of months but they may suddenly vary for no apparent reason, and in a period of more than 2 weeks this variation may compound itself to a serious bleeding level on the one hand or to an even more dangerous clotting level on the other. It, of course, may be necessary to obtain more frequent determinations if the level fluctuates beyond the therapeutic limits. Especially during the early stages of therapy, the prothrombin may rise above the upper limit of the control bracket. Until it is again brought within that bracket supplemental heparin should be given.

TABLE III.—INDICATIONS FOR USE OF LONG TERM ANTICOAGULANTS

Diagnoses	*No. of cases*
Myocardial infarction	17
With cerebral thrombosis	1
With pulmonary embolism	1
Thrombophlebitis	
Lower extremities, recurrent	12
Lower extremities, acute	4
Upper extremity, recurrent	1
Upper and lower extremities, recurrent	1
Lower extremity, acute, and cerebral thrombosis	1
Retinal vein occlusion or threatened occlusion	14
Embolism from the heart to the systemic arterial circulation	10
Arteriosclerosis, lower extremities	4
Retinal atherosclerosis	1
Cerebral thrombosis	1
Pulmonary embolism	2
Total	70

In this series the two stage assay was routinely used to control the prothrombin levels. The advantages and disadvantages of the various prothrombin methods have been presented elsewhere (1) and further discussion of this problem is beyond the scope of this article. The availability of both assays provides a high degree of accuracy and safety in the control of prothrombin depressants.

Once their prothrombin levels are controlled, patients are allowed to travel at will. Special printed instructions are provided the patient who leaves the city to guide him and any physician who may attend him in an emergency, and he is given special tubes and mailing cartons for the periodic return of his blood to the laboratory. It travels well by air, even from foreign countries and except in extremely hot weather the two stage results are little changed in travel of the sample over a period of 48 hours.

INDICATIONS AND CONTRAINDICATIONS

The indications for the use of long term anticoagulants in the 70 cases in this series are listed in Table III. It will be noted that 19 patients had coronary heart disease alone

or in combination with other thrombotic processes, 19 had thrombophlebitis, 14 had retinal vein occlusions, and in 10 instances there had been embolism to the systemic arterial circulation (8 of these had rheumatic heart disease with atrial fibrillation).

The contraindications to anticoagulant therapy respected by us and our associates are blood diseases with bleeding tendencies, severe hepatic disease, and severe renal disease. The presence of an active gastric or duodenal ulcer is also a contraindication, and a history of an ulcer a relative—although not an absolute—contraindication.

AGE AND SEX

The youngest patient in the group was 19 years of age when treatment was instituted and the oldest was 82. There were 4 patients in the third decade, 5 in the fourth decade, 4 in the fifth decade, 21 in the sixth decade, 20 in the seventh decade, and 14 in the eighth decade.

Forty of the patients were males and 30 were females.

FACTORS INFLUENCING CONTROL

Factors influencing the control of anticoagulants can be grouped under the following headings: (1) the physical status, intelligence, and co-operation of the patient; (2) the laboratory methods of control; (3) the properties and characteristics of the various anticoagulants; (4) other drugs and agents administered during anticoagulant therapy; and (5) the experience of the attending physician with anticoagulant therapy.

The patient is an important influence on the control of his therapy. The rigidity with which he follows his instructions both as to dosage of the drug and regular return to the laboratory is most important. A good nutritional state and a relatively normal liver function are necessary. In this latter connection it is preferable that the patient abstain from alcoholic beverages while receiving anticoagulant drugs. We have observed that alcohol definitely influences the tolerance of the patient to the drugs, at times apparently stimulating prothrombin production. Patients who desire small amounts of alcohol are urged to take the same portions daily and on such a routine can be regulated satisfactorily. Further thromboembolic episodes appear in some instances to influence the tolerance of a patient to anticoagulants. We have seen 2 patients on extended anticoagulant therapy whose maintenance doses of anticoagulant drugs rose strikingly following pulmonary embolisms occurring during transient interruption of therapeutic control.

The methods for controlling the administration of anticoagulants are highly important and as stated earlier, discussion of them is not within the scope of this article. However, until methods for determining the effect of prothrombin depressants have been rendered less variable and the more reliable ones less involved technically they will be the subject of controversy.

The anticoagulant selected in the individual case will influence the control. Varying periods of delay in induction and recovery characteristic of different drugs make for ease or difficulty in the regulation of the prothrombin level. Drugs with rapid induction and rapid recovery periods such as tromexan, phenylindanedione, and sintrom provide relatively early control and relative safety from hemorrhage. It is important that these drugs be administered at frequent intervals (in the case of phenylindanedione preferably twice daily) in order to prevent periods of "escape." The use of drugs with short induction and longer recovery periods such as dipaxin and coumadin sodium (warfarin) obviates this difficulty but places a heavier responsibility on the physician to be particularly cautious about overdosage. Vitamin K-active substances provide adequate safety in most instances regardless of the drug used.

Drugs other than the anticoagulants, particularly the methylxanthines, and, as mentioned, alcohol, will bring about a rise in the prothrombin level. We have observed

appreciable elevation of prothrombin levels by drugs containing caffeine and theophylline. In our experience digitalis and the various penicillin compounds exhibit little if any effect on the tolerance of a patient to anticoagulants. Since some of the breakdown products of salicylates are coumarin compounds, such drugs must be given cautiously to patients receiving prothrombin depressants. We have observed depression of the prothrombin level to the point of hematuria in patients on anticoagulant therapy who took large doses of aspirin during upper respiratory infections.

It goes without saying that the experience of the physician with anticoagulant therapy, in general, and with the individual drug, in particular, is an important factor in the proper control of therapy.

EFFECTIVENESS OF THERAPY

Recurrent thrombophlebitis is one of the more important indications for long term anticoagulant therapy, and from the point of view of the results obtained it is one of the most satisfactory conditions treated. This is not infrequently a disease of young adults and may be an important cause of disability and economic loss. In our series 14 patients received therapy for a total of 367 months, with excellent results in 13 of these during the period of administration of anticoagulants. One failure occurred in a man of 26 years in whom a diagnosis of probable Buerger's disease was later made. There was no recurrence after tobacco was stopped. In 1 young woman of 19, apparently protected during 19 months of therapy, the condition recurred 3 weeks after therapy was stopped. Five months of therapy subsequently have been protective. A young man of 28, a carpenter who had had multiple recurrences, some of them while on apparently ineffectively controlled therapy in another hospital, has had no recurrences in 3⅓ years of controlled therapy. A 76 year old female with thrombophlebitis and postoperative pulmonary embolism was free of symptoms during 8 months of anticoagulant treatment. However, 3 months after the drug had been stopped, another classical episode of pulmonary embolism took place, anticoagulant therapy was resumed, and in the past 2 years she has had no embolic events.

Ten patients with atrial fibrillation and peripheral arterial embolism received therapy subsequent to an embolic event for a total of 386 months. Six of these patients had no symptoms of further emboli during treatment. In 1 case there was a probable recurrence while the patient's prothrombin level was 37 per cent. She has had no further emboli in 17 subsequent months with a prothrombin maintained between 10 and 20 per cent. One 83 year old patient had 2 recurrences (1 requiring surgical removal) during 2 "escape" periods in which her prothrombin levels rose above the therapeutic range indicated in the foregoing. She has had none while controlled over a total of 30 subsequent months. Another patient, 34 years of age, had 2 embolic recurrences during periods, also when her levels were uncontrolled. The first, to the iliac artery, followed 1 week after the successful removal of a femoral arterial embolus. The prothrombin was 67 per cent at the time and supplemental heparin had not been given. Successful embolectomy was again accomplished and immediate control established. No further emboli occurred until the anticoagulant was stopped 39 months later to permit mitral commissurotomy. Three days following surgery while heparin was being administered cautiously and inadequately she developed a pulmonary embolism—fortunately not fatal. This patient subsequently developed metrorrhagia while on continuous anticoagulant therapy, and a carcinoma of the body of the uterus was discovered on curettage. Finally, a 71 year old man with severe hypertensive heart disease, atrial fibrillation, and an embolism to the left popliteal artery died quite suddenly 11 months after beginning treatment with anticoagulants. The cause of his death is not known but the gravity of his heart disease would favor a primary cardiac basis.

Recurrence was present in 4, in all instances when the patients' prothrombin was above the 30 per cent level—by design or by accident. It is clear that during the periods of adequate administration of anticoagulants no recurrence of embolism was observed. The effectiveness of the prophylactic treatment of peripheral arterial embolism with *properly controlled* anticoagulants is one of the most convincing bits of evidence in favor of this type of therapy.

The indication for anticoagulant therapy in peripheral atherosclerosis is not clear. If the final occluding factor is a thrombus as would seem to be the case in many instances and if the potential of this factor can be reduced to any degree by anticoagulant therapy—as at this time seems likely—then it would appear to have some rationale. Further considerations are the possible relation of clotting to the formation of atheroma, and the relation of phospholipids to the clotting mechanism. The interpretation of the results in our series of 4 patients receiving treatment over a total of 144 months is difficult. All have extensive atherosclerosis, clinically, arteriographically, or both. None was considered a candidate for grafting procedure, 3 had had a sympathectomy, and 1 had trophic changes. Since anticoagulants were started all have engaged in their usual activities, and there have been no clinical or anatomic evidences indicating a progression of arterial insufficiency. A longer period of time and a much larger number of cases will be required before conclusions can be drawn as to the effectiveness of this type of therapy in atherosclerosis.

Eight patients with 1, and 9 with 2 or more myocardial infarcts are included in this series, as well as 1 patient with myocardial infarction and cerebral thrombosis and 1 with myocardial infarction and pulmonary embolism. Twelve patients have done well with an average follow-up period of 32 months and are continuing treatment. It is possibly significant that angina pectoris has lessened to a striking degree in 4 of these. One patient died several months after he had moved away and had stopped treatment, and another died in heart failure after 7 months of therapy. Another 74 year old patient with a history and postmortem evidence of 3 myocardial infarcts died of bacterial endocarditis with associated cardiac failure after 4½ years of treatment, during which no further infarcts had occurred. Four of the 19 patients constituted true failures. In one 62 year old patient, a second nonfatal infarct occurred at a time when the prothrombin level was 17 per cent, and a 42 year old physician suffered a second nonfatal infarct when his prothrombin level was 26 per cent. In addition, a 59 year old diabetic patient with a history of 2 prior infarcts died from a third infarct 6 years after therapy had been begun, and a 59 year old male with 2 prior infarcts succumbed from a third infarct after 4 years and 9 months of treatment. We do not believe that definite conclusions as to the efficacy of the drugs employed can be drawn from such a small series, but in view of the unfavorable character of the group studied, we are inclined to be encouraged.

Until recently there was little to offer the patient with retinal vein thrombosis. Glaucoma and loss of the eye (usually within 8 months of onset) were usual sequences. In the 14 cases reported here the results as to prevention of blindness and clearing and return of vision were considered good to excellent by our ophthalmologists in 11 patients. Glaucoma did not develop in any instance. In 1 case in which therapy was begun 2 weeks after the onset of symptoms, central vision deteriorated from 20/200 to 2/200 with pitting and scarring of the macula owing, in the opinion of the attending ophthalmologist, to pretherapy intraocular hemorrhage. Peripheral vision was preserved and glaucoma did not develop. Impending occlusion in the other eye was apparently reversed. There were periods of "escape" from therapeutic prothrombin levels in the early stages of therapy, and these have been considered a possible factor in this failure. In a second case, the results were considered

to have been inconclusive as, although vision was preserved, in retrospect there appeared some doubt as to the nature of the vascular changes. A third 71 year old patient died with a cerebral hemorrhage after 21 months of treatment. (Her case will be discussed under "complications.")

COMPLICATIONS

Bleeding was the most frequent complication in this series. Four episodes of gross hematuria occurred in 3 patients, in each instance when the two stage prothrombin level was less than 10 per cent. The hemorrhage was readily controlled by temporary withdrawal of the anticoagulant combined in 3 instances with intravenous administration of a vitamin K preparation.

Two patients incurred large hematomas of the buttock following falls, and a third patient developed a hematoma of the forearm as the result of an automobile accident. All of these resolved spontaneously. Still another patient was in a serious automobile accident, received multiple lacerations at a time when his prothrombin level was 24 per cent, yet suffered no excessive hemorrhage.

In 2 instances, in patients aged 34 and 42 years, metrorrhagia occurred at times when the prothrombin levels were within the therapeutic range. Curettage disclosed the presence of carcinoma of the body of the uterus in both cases. Unexplained uterine bleeding encountered during anticoagulant therapy should alert the physician to the possibility of malignancy.

One woman, aged 71, with retinal vein thrombosis and hypertension, developed a fatal cerebral hemorrhage while receiving anticoagulant therapy. The prothrombin level was 14 per cent 19 days prior to her death, and the patient had failed to return for her scheduled prothrombin determination. It is impossible to determine the role of the anticoagulant in the initiation of the hemorrhage, but it doubtless contributed to the magnitude of the bleeding and may have been a critical factor in the fatal outcome. Another patient, aged 67 years, being treated for recurrent thrombophlebitis, developed a hemiplegia and died some months later. A clinical diagnosis of cerebrovascular accident, either hemorrhage or thrombosis, had been made. Supplemental heparin given intravenously in what was probably excessive doses may have contributed to this complication.

DISCUSSION

It is our belief, as the result of these and other experiences, that the long term administration of anticoagulants can be accomplished safely and effectively in properly selected cases. A prime consideration must be safety. It is apparent from our data that 1 patient suffered a fatal cerebral hemorrhage while receiving anticoagulants, and in another case death may have been contributed to by a possible although unproved similar event. This would appear to represent a serious and even critical argument against the long term use of these drugs. It must be kept in mind, however, that whereas 1 and perhaps 2 lives were lost among the 70 individuals in the series because of uncontrolled hemorrhage, many lives may also have been saved and much disability prevented. This is notably true among patients with atrial fibrillation and peripheral arterial embolism. Further, it must be recalled that the 1 proved fatality occurred at a time when the patient had failed to follow her instructions to return for her routine periodic prothrombin determination. It is also possible that the therapy was not a factor in the initiation of the hemorrhage, though it undoubtedly was an important factor in the fatal outcome. It is our opinion that in such cases there is as much and probably more risk from death due to failure to maintain adequate depression of the prothrombin level, as there is hazard from hemorrhage accompanying excessive anticoagulant effect.

One should not, however, embark upon the use of anticoagulants lightly. First, the physician must himself be familiar with the characteristics of, complications possible

from, and antidotes to the use of such agents, or must have proper professional guidance from someone who possesses this knowledge. Second, a laboratory must be available which can perform consistently reliable prothrombin determinations. In our opinion, this is the major factor in the safety or lack of it and in the extremes of opinions among clinicians regarding the use of anticoagulants. If these two requirements are not met, no patient should under any circumstances receive long term—or indeed short term—therapy with anticoagulants. Third, as we have indicated, the patient must have a disease known or believed to be favorably affected by these agents and, furthermore, must not present one or more of the known contraindications.

Contrary to some expressed opinions, we believe that there are only very rare patients who cannot be controlled on a regimen of anticoagulant therapy. "Failures" usually result from a lack of appreciation of duration of action of such drugs, of the need for routine and frequent check on the prothrombin level, and of the requirement of adequate depression of these levels below 30 per cent, and occasionally below 20 per cent. As we have mentioned, our technical failures were the result of failure to maintain a proper lowering of the prothrombin level. It is not always possible to achieve this with one drug over a prolonged period of time. If undue instability of levels is demonstrated, we have found it wise to question the patient carefully as to the ingestion of alcohol, salicylates, or other substances which may in themselves influence prothrombin levels, and may in the absence of such interfering factors find it wise to shift to another drug to achieve greater uniformity of control. It is undoubtedly true that different drugs in a variety of ways and degrees affect clotting factors other than prothrombin. Such influences are still poorly understood but doubtless are important in the safety and effectiveness of the various drugs, and in their ease of control or lack of it.

The effectiveness of long term anticoagulant therapy for the conditions cited in this article has been discussed. It is our opinion that in recurrent thrombophlebitis, embolism from the heart and venous circulation, and early retinal vein occlusion or impending occlusion, the use of anticoagulants is often crucial in saving the life of the patient or in preventing serious disability. Our experiences with varied atherosclerotic diseases including myocardial infarction is limited and we are pursuing this aspect of the problem further to obtain more satisfactory data over a longer period of observation.

SUMMARY

Seventy patients suffering from various thromboembolic conditions have been given oral anticoagulants over periods varying between 6 months and 9 years. Only those patients whose prothrombin levels as measured by the two stage method averaged less than 30 per cent of normal were included in the study.

Conditions for which the patients were treated included myocardial infarction, thrombophlebitis, retinal vein occlusion, real or threatened, peripheral arterial embolism, peripheral arteriosclerosis, retinal atherosclerosis, cerebral thrombosis, and pulmonary embolism.

Effectiveness of therapy, including failures (true and technical), factors influencing control, and complications are discussed. General and specific problems in the maintenance of patients on long term therapy are given special attention.

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DIAGNOSIS AND TREATMENT OF DIASTEMATOMYELIA

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SINCE 1624, congenital divisions or apparent duplications of the spinal cord have been frequently described in isolated autopsies of fetuses, stillborn monsters, and infants who succumbed shortly after birth. These anomalies were usually found associated with multiple central nervous system and other severe malformations. Ollivier in his *Traité des maladies de la moelle épinière* (1837) described a case which presented an extensive cleft of the spinal cord extending from the fourth dorsal vertebra to the sacrum, and he gave the name of diastematomyelia to this malformation. He differentiated diastematomyelia (Greek: *diastema* cleft, *myelos* medulla) from diplomyelia (Greek: *diplos* double, *myelos* medulla); i.e., the segmental longitudinal division of the spinal cord into two portions from a duplication of the cord. However, it is only in the past 20 years that this condition has been recognized during life as a cause of neurologic disturbances, and its accurate clinical as well as roentgenologic diagnosis and successful surgical treatment are less than 10 years old. The successful case reports of Hamby, Herren and Edwards, Marr and Uihlein, Maxwell and Bucy, Campbell, Pickles, and finally Matson, Woods, Campbell, and Ingraham drew the attention of pediatricians and neurosurgeons to this interesting malformation, its diagnosis, and surgical treatment. A characteristic feature of the malformation is the projection of a bony, cartilaginous or fibrous septum from the posterior surface of the vertebral body through the middle of the spinal canal and a segmental longitudinal division of the spinal cord and the meninges into two separate structures. Most important for the diagnosis were the distinguishing radiographic and myelographic features reported by Walker, Neuhauser, Wittenborg, and Dehlinger, and Cowie (5, 6).

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In the past 2 years, 5 verified cases of diastematomyelia were diagnosed and were treated at University Hospitals of the State University of Iowa. Two other suspected cases did not require surgical treatment and are being followed clinically. All cases presented obvious cutaneous defects, underlying defects of the spinal canal, and associated neurologic disorders. They thus presented the cutaneous, mesodermal, and neural forms of spinal dysraphism discussed by Lichtenstein. Diastematomyelia is more frequently seen in females than in males (ratio 4:1) during infancy and early childhood. Although born with obvious cutaneous as well as bony and neural anomalies, the neurologic disorders become most evident when the child starts to walk and become more obvious with age, attracting the attention of parents and physicians. The symptoms depend upon the location and the extent of the malformation but most commonly develop in one or both lower extremities. They consist of weakness, atrophy, maldevelopment and malformation, with associated disturbances of gait and stance, disturbance of sensation, reflex changes, impaired function of the bladder and rectal sphincters, and secondary infection, ulceration, and trophic changes of anesthetic areas. In the following 5 cases the diagnosis of congenital spinal anomaly was made from clinical examination of the patient. However, the diagnosis of diastematomyelia and its exact location depended upon the roentgenologic and myelographic examinations and verification at operation. In 1 case the diastematomyelia was associated with an infected thoracic myelomeningocele and was not diagnosed preoperatively. It presented many

FIG. 1. Case 1. Roentgenograms showing the fusiform widening of the lower thoracic spinal canal, fusion of the ninth and tenth thoracic bodies, and a suggestive bony spicule arising from the posterior aspect of the body of the tenth thoracic vertebra.

features similar to the case described by Weil and Matthews. Because of the presence of the myelomeningocele, myelography was not considered necessary.

CASE REPORTS

CASE 1. This 3½ year old girl was admitted to the University Hospitals on March 22, 1954, with a 6 weeks' history of fever, vague pains in her extremities, and a tentative diagnosis of subacute bacterial endocarditis. Previous to her admission she had spent 6 weeks in another hospital with fever, persistent vomiting for several days, inconstant heart murmurs, high sedimentation rates, anemia, and leucocytosis. The electrocardiogram was normal. Blood, urine, and nose and throat cultures were negative. Agglutination tests for typhoid and brucellosis were negative. The tuberculin test was negative. She was vigorously treated with sulfonamides and antibiotics and was given 2 blood transfusions.

The patient was born on August 3, 1950, the first child of a healthy mother, aged 21 years. Pregnancy and delivery were assertedly uncomplicated.

Examination revealed a co-operative, mentally alert, but chronically ill child. No heart murmurs could be heard on auscultation. Generalized muscle tone was poor. She had no pain over her spinal column and no neck rigidity. A tuft of long hair was present over the midline of the back in an area covering the eighth, ninth, and tenth thoracic vertebrae. There was no evidence of other skin lesions over the spine. According to the mother, the child was born with this tuft of hair. However, it had grown since birth and become more profuse. Both lower extremities were weak and their muscles were poorly developed. She could stand only with support. The deep reflexes were brisk and equal. There was an occasional right ankle clonus. She had no pathologic reflexes. The abdominal reflexes were equally brisk. Sensation appeared intact over the entire body including the lower extremities. She had a persistent temperature of 101 degrees F. and a leucocytosis. The urine was normal. There was blood in her stools. Heterophile, brucellosis, and typhoid agglutination tests were negative. Blood cultures were sterile. Urine cultures were also sterile. Sedimentation rate was increased. Spinal puncture revealed a pressure of 140 millimeters of water, free dynamics, a protein of 16 milligrams per cent, and a sugar content of 65 milligrams per cent. Roentgenograms of the paranasal sinuses and of the chest showed no evidence of old or recent infection. Intravenous pyelograms were normal. The electrocardiogram was also normal.

X-ray films of the dorsolumbar spine demonstrated a widening of the interpedicular space of the eighth, ninth, and tenth thoracic vertebrae with failure of fusion of the left side of the posterior arch of the ninth thoracic vertebra. The body of the ninth thoracic vertebra was smaller than the vertebrae above and below and the intervertebral disc space between the ninth and tenth thoracic vertebrae was narrow. Overlying the center of the tenth thoracic vertebra in the anteroposterior projection was a shadow suggesting a spicule of bone which on the lateral view was seen to pass obliquely upward posteriorly (Fig. 1). A roentgenologic diagnosis of diastematomyelia was made. There was some doubt that the spinal cord defect could be responsible for the patient's fever and her anemia, especially with grossly negative spinal fluid studies not indicative of meningeal irritation. However, it was thought that the vertebral defect and the diastematomyelia might be responsible for the weakness in the lower extremities.

Laminectomy of the eighth, ninth, and tenth thoracic vertebrae was performed on April 1, 1954. The spinous processes of the eighth and ninth thoracic vertebrae were fused together and the laminal arches of the eighth and ninth thoracic vertebrae were also fused. There was a large amount of extradural fat which was later reported histologically as normal. Only one dural canal was encountered. The arachnoid appeared thin and transparent. No anomalies of the spinal cord were seen. The cord could be rotated without difficulty, and no bony spicule intruding into the anterior portion of the vertebral canal was found. A catheter was then passed up and down the subarachnoid space without meeting any obstruction. The patient's postoperative condition was good. On the same day another x-ray study of her dorsolumbar spine was made and showed the laminectomy to have involved the twelfth, eleventh, and tenth thoracic vertebrae. The suspected bony spicule was again seen rising from the upper border of the tenth thoracic

vertebra. On April 9, 1954, myelography was performed and a smoothly rounded, constant area of radiolucency in the midline of the opaque column at the level of the eighth and ninth thoracic vertebrae was demonstrated. It corresponded with the suspected bony spur and the previous roentgenologic diagnosis of diastematomyelia was confirmed.

The patient was reoperated upon on April 12, 1954, when a laminectomy of the seventh, eighth, and ninth thoracic vertebrae was performed. A large amount of extradural fat was again encountered. No obvious duplication of the dural sac was seen. However, at the level of the ninth thoracic vertebra a dimple was present in the midline of the dura resembling an umbilicus, and it contained a prominent pink central elevation surrounded by a coronal sulcus (Fig. 2). This structure was firmly connected with the arachnoid and the spinal cord. It was transected posterior to the surface of the cord and resected with surrounding dura. This structure continued anteriorly and traversed the cord completely. There was a slit-like division of the cord into two halves for a distance of 2 centimeters. The cord was surrounded by arachnoid and dura. The posterior spinal artery traveled to the left and gave off a branch which disappeared into the anomaly. Attempts to rotate the cord from one side to the other disclosed adherences to the anterior dura. Following transection of the seventh and eighth posterior thoracic roots and the denticulate ligaments, the cord could be slowly elevated and slightly rotated to the left. The spicule of bone, which had the gross appearance of a rose thorn, was covered with dura, arose from the midline of the anterior surface of the spinal canal and penetrated the cord. The apex of the thorn was directed toward the head and its course was an oblique one. The bony spicule measuring approximately 6 millimeters in height was rongeured away. Immediately caudad to the base of the bony spicule, the anterior extension of the fibrous structure which crossed the spinal cord could be visualized. It arose from the underlying dura. This structure was cut close to the cord and resected. The patient's operative and postoperative condition remained good. Her wound healed without complication. Curiously enough, she was free of fever following the second operation and was discharged from the hospital on April 19, 1954, with some weakness in both lower extremities, normal reflexes, absent ankle clonus, and good bladder control. The umbilical-appearing structure transfixing the cord consisted of dense layers of collagenous tissue enclosing several dilated venous channels filled with blood, and it was thought to be dura.

The patient was readmitted on December 28, 1954, with fever and swollen joints. At this time a diagnosis of rheumatoid arthritis was made. Repeated blood and spinal fluid cultures were sterile. A further electrocardiogram was normal. Neurologically her strength had greatly improved in the lower extremities. She had good bladder and bowel control. At her last check-up examination (September 15, 1956) the tuft of hair was still present and needed cutting once a year. She had no neurologic symptoms or signs.

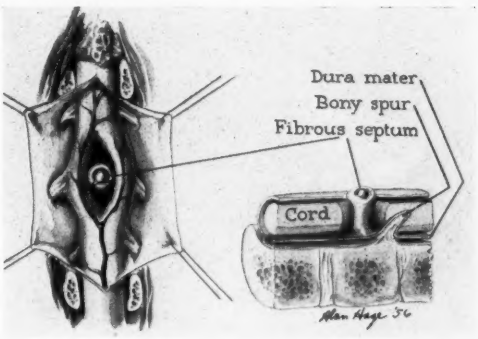

FIG. 2. Case 1. Drawing representing the operative findings of a bony spur penetrating into the cord and a fibrous septum dividing the cord.

The characteristic finding of a tuft of hair over the lower thoracic spine associated with weakness of both lower extremities suggested the presence of an underlying spinal anomaly. Roentgenograms of that region showed congenital anomalies of the vertebrae and the presence of a spicule arising from the superior posterior portion of the body of the tenth thoracic vertebra. The myelograms confirmed the presence of a defect in the subarachnoid space at that same level. Both roentgenographic findings were characteristic for diastematomyelia and were confirmed by the operative findings: the bony spicule arising from the posterior surface of the vertebral body and penetrating the spinal cord, covered by dura, associated with a thick strand of fibrous dura which transfixed the spinal cord in its midline and united the posterior aspect of the dura with its anterior aspect. It is doubtful that this malformation was responsible for the patient's febrile symptoms which brought her to the hospital.

CASE 2. This 1½ year old boy was first seen at University Hospitals on May 25, 1954, for a congenital deformity of the left foot. He was born on September 1, 1952, the third child of a 24 year old mother, after an uneventful pregnancy and labor. A few days after

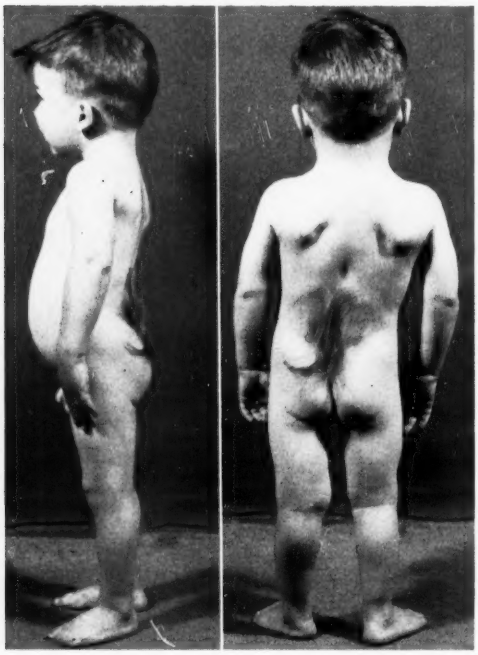

FIG. 3. Case 2. Photograph of the 1½ year old patient showing the hypertrichosis, skin dimple, and slight shortening of the left leg.

birth the parents noticed that the child's left foot was turned in and slightly smaller than the right. Since birth the left foot had grown but had remained smaller than the right. The child started to walk alone at the age of 14 months at which time the parents noticed that he was dragging the left foot. They also stated that the left foot was cooler than the right and that there seemed to be no sensation over the dorsal aspect of the left foot. He was also born with a tuft of long, fine, brown hair over the midline of the lumbosacral region. The hairs had increased in length but the patch had not increased in size since birth.

Examination revealed a well nourished, co-operative child in good general health. A large area of 12 inch long silky hairs was present over the entire lumbar spine (Fig. 3). The child dragged the left foot when walking. He occasionally walked on the lateral aspect of the foot. The left lower extremity was 1 centimeter shorter than the right. There was weakness of the plantar flexors and dorsiflexors of the left foot and toes, and there appeared to be sensory loss below the level of the left knee. He maintained the left foot usually in an abduction position. The left patellar and Achilles reflexes were absent. The abdominal and the cremasteric reflexes were present bilaterally.

X-ray examination of the spine demonstrated a spina bifida with widening of the pedicles starting at the tenth thoracic vertebra and involving all of the lumbar and sacral vertebrae. The greatest widening of the interpedicular distance was noted between the twelfth thoracic and the first, second, and third lumbar vertebrae. The left posterior arches of the eleventh and twelfth thoracic and first lumbar vertebrae were irregularly formed. The lateral portions of the eleventh and twelfth ribs were fused on the left side. The presence of a diastematomyelia on a cartilaginous basis was suggested.

The child was seen in the orthopedic department and was given an outer heel wedge to be used on the left shoe. One month later he had developed an infection with redness and swelling in the left fifth toe and over the dorsum of the foot. His gait showed external rotation and slight limp of the left foot which tended at times to invert, resulting in frequent turning of the ankle. Anesthesia in the area of the fifth lumbar and first and second sacral dermatomes favored injury of the skin of the lateral margin of the left foot and the fifth toe. Skin ulceration and beginning necrosis of the fifth toe were present. A slight scoliosis of the lower thoracic and lumbar spine with convexity to the left was palpable. About 1 inch superior to the upper border of the hairy growth, a defect in the spinous process of the lower thoracic vertebrae was palpated. A clinical diagnosis of diastematomyelia was made. Spinal puncture under general anesthesia revealed an initial spinal fluid pressure of 260 millimeters of water and free dynamics. The fluid contained 2 lymphocytes per cubic millimeter and a protein of 24 milligrams per cent.

Myelography revealed the formation of two separate opaque columns, one on each side of the widened spinal canal extending from the first lumbar to the ninth thoracic vertebra. The two columns merged into one above the ninth thoracic and below the first lumbar vertebra suggesting a diastematomyelia (Fig. 4).

A laminectomy of the first lumbar and twelfth, eleventh, and tenth thoracic vertebrae was performed on July 16, 1954. The spinous processes of the eleventh and twelfth thoracic vertebrae were found to be closely and firmly connected by fibrous tissue. There was no first or second lumbar spinous process. Part of the posterior arch of the first lumbar was present but the arch was absent at the second lumbar vertebra. A thick ligamentum flavum bridged the spina bifida defect. A large amount of extradural fat was present. The spinal canal was wide and appeared flattened. The dura looked grossly normal, but there was a ridge of fibrous tissue in the midline over the dura at the level of the eleventh and twelfth dorsal vertebrae. The dura was opened in the midline, and a clear transparent arachnoid filled with fluid was observed. The ridge of fibrous tissue seen over the posterior aspect of the dura extended into the subarachnoid

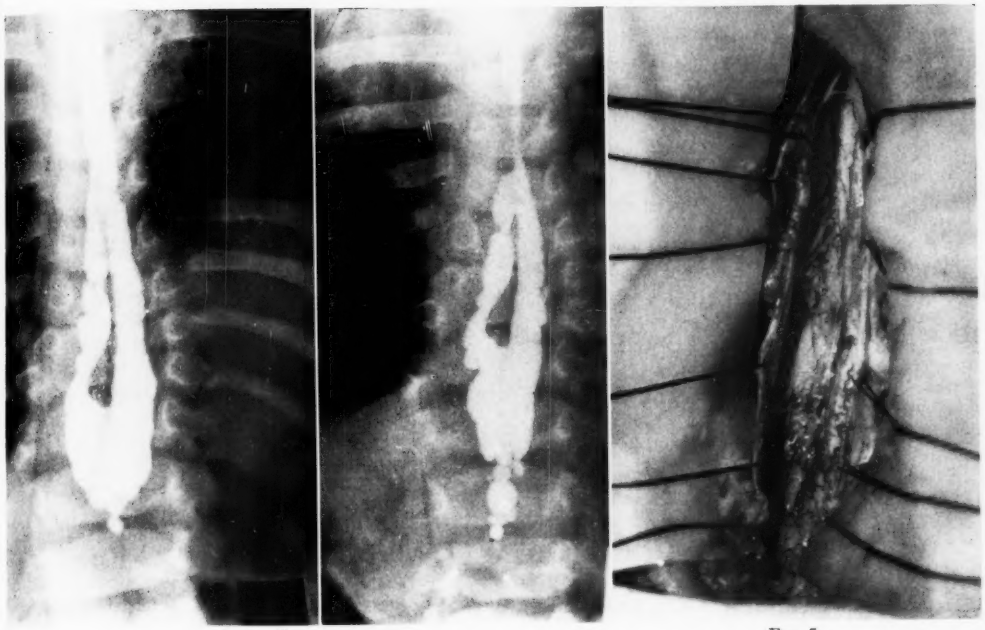

FIG. 4.

FIG. 5.

FIG. 4. Case 2. Myelograms outlining the split in the subarachnoid space produced by a fibrous septum. Notice the widening of the spinal canal and rib anomaly.

FIG. 5. Case 2. Photograph of the split spinal cord seen at operation, after removal of fibrous septum.

space. The arachnoid membrane was connected to it, and it extended through the center of the spinal cord so as to split it from the tenth thoracic to the first lumbar vertebra (Fig. 5). This fibrous tissue grossly appeared like dura. Several anomalous arachnoidal adhesions containing blood vessels were present. Each half of the split spinal cord was surrounded by a separate arachnoidal sac. The cord was rotated from left to right and elevated from its floor after section of the denticulate ligaments. To free the cord completely it was necessary to resect the two lower fascicles of the wide twelfth dorsal motor root. Through an elongated defect in the anterior aspect of the dura protruded a septum of fibrous tissue which transfixed the cord and was continuous with the one seen posteriorly. It was thought that fibrous tissue probably arose from the posterior spinal ligament through a dural defect. Numerous blood vessels accompanied it. The fibrous septum was severed at the base where it emerged through the dura, pulled through the cord, and removed.

The child's condition remained good during and after operation. His wound healed without complication. He developed temporary urinary retention and some abdominal distention. When discharged on July 25, 1954, the neurologic picture had not changed. The left Achilles and patellar reflexes were absent, and there was anesthesia over the lateral aspect of the left foot and the anterolateral aspect of the left leg. The patient walked with a 45 degree external rotation of the left foot and leg. He was voiding normally. Later examination revealed still some generalized slight atrophy in the left lower extremity. The left fifth toe was completely healed but the nail was absent. The fine long hair was again present over the lumbar region. Analgesia was present over the lateral aspect of the left leg and over the entire left foot. He was still walking with eversion of the left foot and leg. Some weakness was present in the plantar and dorsiflexors of the left toes. The left patellar and Achilles reflexes were present but diminished.

This case of diastematomyelia presented lower motor neuron signs involving the left lower extremity, extensive spinal anomalies, growth of hair over the spina bifida occulta in the lumbar region. The diastematomyelia was suggested by the roentgenographic anomalies of the lower thoracic and lumbar spine, especially the widening of the interpedicular space above the spina bifida. The

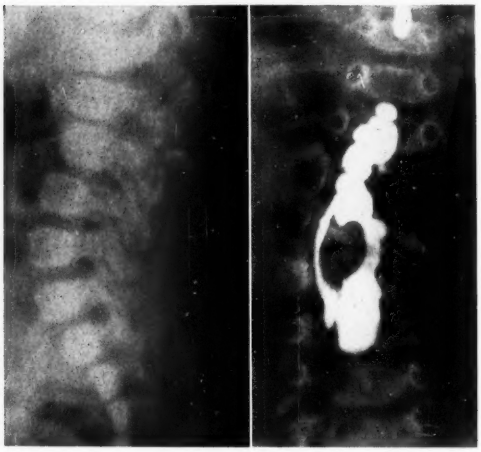

FIG. 6. Case 3. Roentgenogram of lower spine showing the bony spur extending posterior to the neural arch and myelogram outlining the asymmetrical split in the subarachnoid canal produced by the bony septum.

diagnosis was confirmed by myelography and at the time of operation the cord was found to be transfixed by fibrous tissue, apparently arising through an anterior dural defect.

CASE 3. This female patient was first seen at the age of 1 month, on March 2, 1955, because of a soft tissue mass over the lumbar region covered by long hair and inversion of the left foot. The prenatal history was uneventful. She was the second child of a 27 year old hypertensive mother and was born by breech delivery on February 1, 1955.

FIG. 7. Case 3. Photograph of patient 5 months after operation showing area of hypertrichosis, difference in size of feet, and weakness in dorsiflexors of left foot and toes.

Examination revealed a poorly demarcated soft tissue mass measuring approximately 3 to 4 centimeters in diameter, covered by long soft hair, over the lumbar spine. There was also a bony protrusion of the neural arch on the left side, and a spina bifida could be palpated in the lumbar region. A small opening was present in the soft tissue mass and had the appearance of the mouth of a sinus tract. The left foot appeared smaller than the right and was kept in inversion.

X-ray films of the lumbar spine were interpreted as showing a spina bifida occulta, and the bony mass was interpreted as a protrusion of a left neural arch in the midlumbar region. Neurologic examination was otherwise grossly normal. It was thought that the soft tissue mass represented a benign growth, probably a lipoma, over the spina bifida. The left foot held in mild equinovarus position could be easily corrected beyond neutral position, and the mother was instructed to stretch the Achilles tendon and the joints of the foot in order to prevent deformity.

The patient was admitted to University Hospitals on August 8, 1955, at the age of 6 months. The left foot appeared smaller than the right. The deep reflexes were less active in the left lower extremity than in the right. Strength, motion, and sensation appeared grossly equal in the lower extremities. There was an area of long hair growth measuring about 5 by 2 centimeters over the second and third lumbar regions. The spinal defect could be palpated in the lumbar region. There was a bony prominence to the left of the midline at about the level of the second and third lumbar vertebrae with a small sinus opening lateral to it. The spinal fluid pressure was normal; the fluid was clear, and the total protein 29 milligrams per cent. Films of the lumbar spine showed a spina bifida involving the twelfth thoracic, the first, second, and third lumbar vertebrae. Myelography revealed a filling defect at the level of the second and third lumbar bodies to the left of the midline (Fig. 6). In its center there was a density thought to represent a bony spur extending through this area and surrounded by soft tissue. The defect was consistent with diastematomyelia.

Laminectomy was performed on August 12, 1955. The region of the spina bifida was uncovered extending from the first to the fifth lumbar vertebra inclusive. At the first lumbar vertebra the two laminae were close to the midline, but at the second and third lumbar vertebral levels they widened, only to come together again at the level of the fourth and fifth lumbar vertebrae. The spina bifida defect, especially in its upper portion, was covered by a large mass of mature and fetal adipose tissue, lobulated by dense fibrous septa and intermingled with striated muscle and connective tissue. A bony mass, which had been felt clinically and interpreted roentgenologically as a bony prominence to the left of the midline, was situated medially and slightly inferiorly to the rudimentary

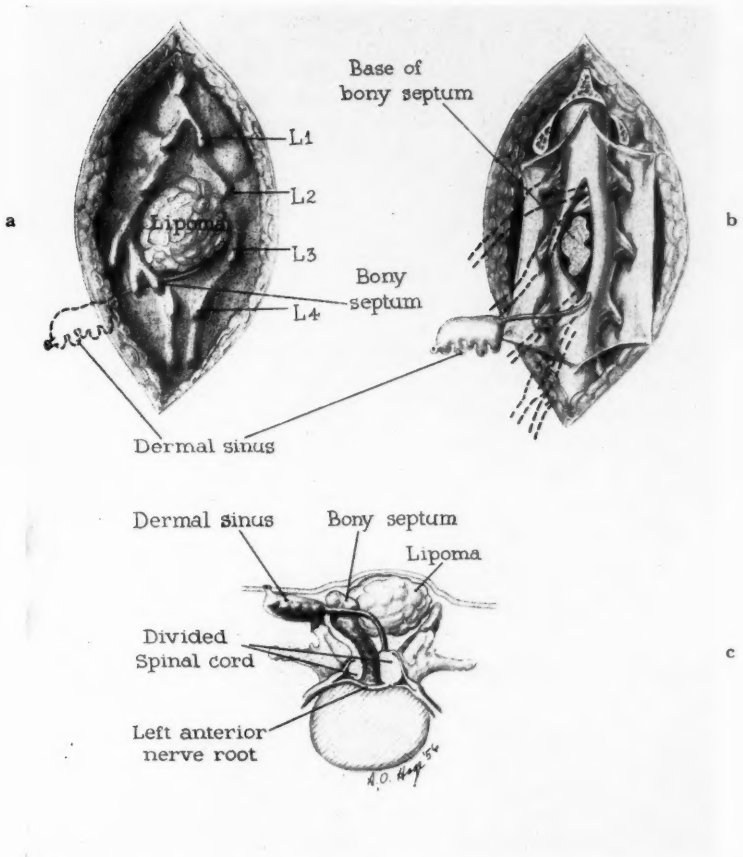

FIG. 8. Case 3. Drawings of operative findings: a, extradural lipoma and posterior projection of bony septum; b, asymmetrical division of spinal cord after removal of bony septum with relation of dermal sinus to spinal cord; c, cross section view of pathologic findings with emphasis on origin and course of anterior and posterior spinal nerve roots in relation to bony septum.

lamina of the third lumbar vertebra (Fig. 8). It seemed to represent an anomalous spinous process and could be followed to the dura. The sinus tract placed inferiorly to this bony mass could also be followed medially to the dura to about the fourth lumbar vertebral level. After completion of the laminectomy and removal of the ligamentous attachment connected to the bony anomaly, it became apparent that this process continued anteriorly so as to split the dural sac into two segments. It seemed to arise from the body of the third lumbar vertebra. A split in the dural column extended from the superior portion of the second lumbar to the superior portion of the fourth lumbar vertebra. Above and below these levels the two dural sacs reunited to form a single dural sac. The sinus tract could be followed down to the most inferior portion of the bony and fibrous island between the two dural canals and was closely associated with the dura and the underlying arachnoid on the right side of the midline. When the dura was opened, two separate spinal cords were visualized, the right one arising from approximately two-thirds of the cross section of the original cord while the left one was markedly thinner (Fig. 8). Both cords were surrounded with arachnoid, and their respective subarachnoidal spaces contained spinal fluid. On both sides vessels could be seen on the pia. The posterior nerve roots arose from the right as well as the left spinal cord while all the anterior nerve roots arose from the right-sided segment. Some passed above and some below the bony island, beneath the left spinal cord segment. The beginning of the conus medullaris could be seen at the level of the fifth lumbar vertebra.

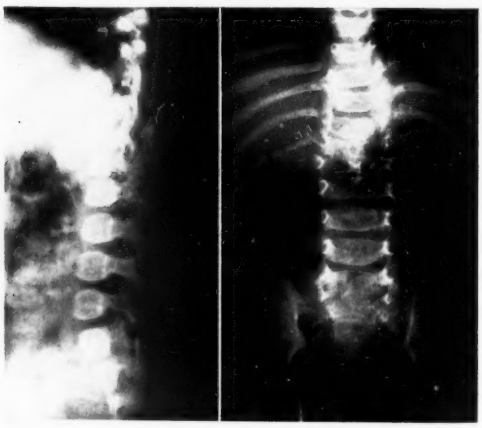

FIG. 9. Case 4. Roentgenograms of lower spine showing widening of lumbosacral canal, fusion of bodies of the twelfth thoracic and first lumbar vertebrae and presence of abnormal bony projection over the twelfth thoracic and first lumbar vertebrae.

The midline septum was then removed as completely as possible including bone, cartilaginous tissue, vessels, and dura. Both halves of the spinal cord were then fully mobilized, and the dura was closed so as to form a single dural canal posteriorly. The child's operative and postoperative courses were satisfactory, and the operative wound healed without complication.

On the first postoperative day the baby moved both lower extremities equally well and appeared to void normally. However, on the second day she did not move the left lower extremity, and on the third day a phlebitis had developed in the previously cannulated left saphenous vein. This complication was associated with fever. The child regained some movements in the left lower extremity on the fourth postoperative day, especially in the thigh. She was discharged on August 23, 1955. Two months after operation the length of the left foot was 1 centimeter shorter than the right. Urination and bowel movements were normal. She moved both lower extremities equally well. Five months after operation she was able to climb up and down stairs without difficulty. The left foot was 1 centimeter shorter and approximately ½ centimeter narrower than the right. The circumference of the left calf was approximately 1 centimeter less than the right, and the left lower limb was ½ centimeter shorter than the right (Fig. 7). The left patellar reflex was absent, the left Achilles reflex diminished. There was no apparent sensory deficit. She was able to stand and kick well. At the age of 14 months it was thought that she did not move the left foot as actively as the right. One year after operation the left lower extremity was slightly smaller than the right, and the left patellar reflex was absent. She had good motion in both feet and toes. However, when walking she dragged the left foot.

This case presented not only a division of the spinal cord but a division of the entire dural canal into two separate canals. The midline septum was larger than that noted in the previous cases and was connected with an anomalous subcutaneous bony projection which was more prominent than the rudimentary lamina of the spina bifida. The split portions of the spinal cord were of unequal width, the right appearing larger and more important than the left. Of interest is the fact that the conus medullaris extended below the fifth lumbar vertebral level. A sinus tract ended blindly in the arachnoid. Diagnostically, this child presented fairly characteristic signs and symptoms such as a marked widening of the interpedicular space associated with a spina bifida, a palpable abnormal bony prominence in the same region, and long tufts of hair covering the skin. The myelographic picture was also diagnostic.

CASE 4. This girl, born June 4, 1954, was first seen in the Crippled Children's Field Clinic on April 13, 1955. She had a congenital clubfoot on the right which was treated by a local orthopedic surgeon. The child also had a growth of hair over the lower thoracic and upper lumbar regions. No muscle weakness was apparent. Roentgenograms of the dorsolumbar spine showed anomalies of the twelfth dorsal and first lumbar vertebrae with widening of the interpedicular spaces and spina bifida extending from the tenth thoracic vertebra to the sacrum. There appeared to be a fusion of the twelfth thoracic and first lumbar vertebrae with narrowing of the eleventh to twelfth thoracic intervertebral disc space. A longitudinal midline bony spur extending from the twelfth thoracic to the first lumbar vertebra was also visualized, and a diagnosis of diastematomyelia was made (Fig. 9).

The child was admitted to the University Hospitals on June 17, 1955. She was the third child of a healthy mother who was 21 years old at the time of pregnancy and whose pregnancy and delivery were assertedly uneventful. The baby was born with a tuft of hair in the dorsolumbar region and evidence of a right-sided clubfoot. However, she was able to move both lower extremities well.

On examination she used the right lower extremity less actively than the left and dragged the right leg when crawling. The left thigh was slightly smaller than the right. She had good muscle strength and no apparent sensory loss in the lower extremities. A large amount of fine hair was present over the dorsolumbar spine with a dimple in the skin overlying the first

FIG. 10.

FIG. 11.

FIG. 10. Case 4. Photograph of patient at age of 1 year showing right clubfoot, thoracolumbar hypertrichosis, and skin dimple.

FIG. 11. Case 4. Photograph of operative view showing large bony septum dividing spinal cord.

lumbar vertebra (Fig. 10). A bony prominence was present in the lower thoracic region. Clubfoot was present bilaterally, more pronounced on the right side than on the left. However, roentgenograms of both feet showed the left to be normal. The patient was treated on the orthopedic service with corrective casts.

Myelography was performed on July 5, 1955, and revealed a split in the column of contrast material at the level of the twelfth thoracic and first lumbar vertebrae. The diagnosis of diastematomyelia was confirmed. Following myelography the child developed high fever with nuchal rigidity. The spinal fluid was cloudy and contained 60 to 100 white blood cells per cubic millimeter; the protein was 75 milligrams per cent, glucose 53 milligrams per cent, and chloride 126 milliequivalents. Cultures, however, remained negative, and it was thought that this child had a chemical meningitis due to pantopaque.

At operation on July 12, 1955, a bony protrusion was found in the midline at the level of the twelfth thoracic to first lumbar vertebra immediately beneath the skin. It was surrounded by dense fibrous tissue, firmly connected with the surrounding fat, muscle fascia, and fibrous tissues covering the spina bifida occulta. Laminectomy and dissection of the midline bony process revealed the presence of two separate dural canals extending from the eleventh thoracic to the second lumbar vertebrae. The bony mass penetrated the area between the two dural canals and measured approximately 2 centimeters in length and 1 centimeter in width. The longitudinal split of the spinal cord and the dural canal extended approximately 2 centimeters above and 2 centimeters below the bony malformation. This process was firmly adherent to the surrounding fibrous tissue and to both dural sacs. It was followed to the anterior aspect of the spinal canal and was seen to emerge from the posterior surface of the fused bodies of the twelfth thoracic and first lumbar vertebrae. The opened dura exposed well the two separate spinal cords, the right one being slightly larger than the left (Fig. 11). The surrounding arachnoid was slightly opaque and adherent to the dura and to each cord. Each half of the cord gave rise to the ipsilateral nerve roots. The posterior and anterior dural defects were closed after complete removal of the bony, cartilaginous, and fibrous tissue dividing the cord. The spina bifida defect was

closed by mobilization and midline suture of the paraspinal muscles and the overlying fascia. The child's postoperative course was uneventful. Her wound healed satisfactorily, although she accumulated some yellowish fluid beneath the skin which had to be aspirated twice. She was discharged from the hospital on July 23, 1955, with a Denis Browne splint for the lower extremity.

Two months after discharge she was manifestly gaining better control in her legs and was able to crawl with her brace on. She could also stand in bed with the brace on. Sensation appeared normal in both feet and toes. She did not have any urinary or anal disturbances.

Check-up examination 10 months after operation showed much improvement in her gait although she still had a tendency to turn the right foot inward. Toilet control was complete. She still had a large patch of hair over the upper lumbar and lower thoracic regions. There were no sensory disturbances in the lower extremities. The reflexes in the lower extremities were bilaterally equal. It was again recommended that the patient wear the Denis Browne splint at night.

The presence of a tuft of hair over the lower thoracic spine associated with an upper lumbar skin dimple and a clubfoot suggested the presence of an underlying spinal cord anomaly. The suspected clinical diagnosis of diastematomyelia could easily be confirmed by the roentgenograms and myelograms of the lumbodorsal region. The large midline bony process arising from the site of fusion of the twelfth thoracic to first lumbar vertebral bodies split the dural canal and its contents into two separate canals for a distance of two full vertebral segments.

Neurologic disorders do not necessarily need to be present. One may even postulate that the more extensive widening of the spinal canal and division of the dural canal may have prevented the development of spinal cord and nerve root symptoms.

CASE 5. This girl was born on September 17, 1955, the second child of a 22 year old mother, and was admitted to University Hospitals on October 18, 1955. Pregnancy and delivery were assertedly uncomplicated. At the time of birth the infant presented a draining myelomeningocele in the midthoracic region. This was surgically dressed for 2 weeks. On examination the child presented a midthoracic myelomeningocele measuring 7 by 4.5 by 2 centimeters covered with a transparent membrane partly replaced by an apparently infected granulating surface oozing cerebrospinal fluid. The head circumference was 37.5 centimeters. The anterior and posterior fontanelles were widely open. The neck appeared unduly short. The patient moved the lower extremities fairly well. Both patellar reflexes were present and equal. There was movement of the feet and toes. However, there was no response to pinprick over the lower extremities, and sphincter tone was absent.

Multiple congenital anomalies of the cervical and thoracic portions of the spine were demonstrated roentgenologically. She had only 5 cervical vertebrae, and the spinous processes of the fifth cervical and first thoracic vertebrae were fused. A spina bifida extended from the midthoracic region to the fourth lumbar vertebra. Several thoracic hemivertebrae were present, more on the right than on the left. There were 11 ribs on the right side and 9 on the left. Some of the ribs were fused on the left. The body of the tenth thoracic vertebra formed two lateral masses. There was also widening of the dorsal and lumbar spinal canal. The diagnosis of thoracic myelomeningocele, multiple vertebral anomalies, and incipient hydrocephalus was made.

Culture of a smear taken from the granulating surface of the myelomeningocele revealed the presence of hemolytic Staphylococcus aureus. The myelomeningocele was then treated locally with bacitracin ointment and 1 per cent acetic acid. The circumference of the head gradually enlarged to measure 42 centimeters. The fontanelles were bulging and tense, and separation of the cranial suture lines was demonstrable. It was planned to treat the hydrocephalus at the time of closure of the myelocele by establishing an anastomosis between the dorsal subarachnoid space and the peritoneal cavity.

At operation on November 15, 1955, the repair of the myelomeningocele was not as simple as expected. Spinal fluid aspirated from the sac contained 153 milligrams per cent of total protein, 58 milligrams per cent of glucose and 120 milliequivalents of chloride. There was no visible residual of infection. The exposed contents of the spinal canal were covered with a thick arachnoid membrane which was adherent to many of the surrounding structures. A hard, large mass was present in the center of the myelocele sac, extending from its surface down to the spinal cord. Pull on this mass, however, produced traction on the visualized nerve roots and the spinal cord proximally as well as distally to that point. At the upper edge of the exposed spinal canal a normal-looking spinal cord was observed. The latter divided into two separate components, the right one appearing somewhat bigger, rounder, and more compact than the left. The two halves of the spinal canal were separated by scar and fibrous tissue which was continuous with the hard mass which had been resected with the dome of the myelomeningocele. The essential structure was that of diastematomyelia although

no obvious bony protrusion arose from the anterior aspect of the spinal canal. Caudad from the site of this septum of fibrotic tissue, numerous normal-appearing nerve roots emerged from a centrally located single spinal cord to form the beginning of the cauda equina. After dissection and preservation of nearly all the nerve elements, an attempt was made at establishing the patency of the spinal subarachnoid space. However, compression of the large protruding anterior fontanelle did not produce a flow of cerebrospinal fluid and probing with a thin French rubber catheter revealed the presence of an obstruction approximately 3 to 5 centimeters cephalad to the operative site. Therefore the intended thoracic subarachnoid-peritoneal anastomosis was not performed. The dura which made up the lateral wall of the meningomyelocele was then dissected off the subcutaneous tissue. It was imbricated over the spinal cord after dissection of the island of fibrous tissue which had split it into two halves. On the left side the vertebral bodies could be palpated; however, on the right they seemed absent. Fascial and muscular closure over the site of the spina bifida was not feasible, and only subcutaneous and skin closure could be effected without tension.

The baby's postoperative condition was at first characterized by abdominal distention which necessitated gastric decompression. The distention of the ventricular system increased and was treated by frequent ventricular punctures. On the eighth postoperative day the child developed fever, and the wound showed evidence of infection. Soon the clinical signs of meningitis developed with high fever, respiratory disturbances, lethargy, and increase in the hydrocephalus. Cultures of ventricular fluid revealed the presence of Pseudomonas aeruginosa. The baby was vigorously treated with antibiotics. No further bacterial growth could be obtained from ventricular fluid cultures after January 10, 1956. The baby's condition gradually improved. Its head circumference had increased to 45.5 centimeters and, when the child was finally discharged on February 10, 1956, measured 44 centimeters. When she was seen 6 months after operation, she showed some weakness and spasticity in the lower extremities. She still had unexplained bouts of abdominal distention associated with rapid respiration.

On July 23, 1956, the head circumference was 47 centimeters. Some movements were seen in the lower extremities only on painful stimuli. The child had also developed a convulsive disorder characterized by extension of all extremities, cyanosis, and dyspnea.

This case of diastematomyelia was not diagnosed preoperatively and was associated with multiple central nervous system anomalies. In the foreground stood the thoracic meningomyelocele and the hydrocephalus. From a roentgenologic point of view, a definite widening of the interpedicular spaces was present. However, it was associated with an obvious spina bifida and myelocele. At operation a definite diastematomyelia was encountered but the tissue between the two halves of the spinal cord was neither bony nor cartilaginous but entirely fibrous and was directly connected to the vertex of the dome of the myelocele.

DISCUSSION

Clinical diagnosis. The majority of the cases reported in the literature showed congenital cutaneous defects over the spine or neurologic disorders or both. Among the 22 cases of diastematomyelia reported by Ingraham and Matson, 5 had no obvious cutaneous defects and 6 had no neurologic disturbances. Only 1 of their cases exhibited no skin or neurologic defects (other than those related to meningeal infection). The majority of patients with spina bifida occulta present no neurologic disorders or cutaneous anomalies. However, if these disturbances should be present and a spina bifida can be detected roentgenologically, the patients deserve further clinical investigation for possible treatment of the neurologic disorder. The association of congenital cutaneous defects, neurologic disorders, and roentgenologic evidence of anomalies of the spinal column should raise a suspicion of the presence of diastematomyelia and clearly requires further investigation.

Cutaneous defects were present in all patients of this series. The thoracic skin defect and the protruding myelomeningocele of Case 5 was obvious and quite readily localized the level of the lesion. The other 4 cases presented localized hypertrichosis characterized by long, soft silky hair lying in the midline of the back, usually over the region of the underlying bony anomaly but not necessarily over the level of the diastematomyelia itself. This abnormal hair growth was present at birth. Associated with this finding 1 patient presented a congenital dermal sinus and a lipoma, and 2 others skin dimples.

Disturbance of fusion of the vertebral neural arch was detected twice. It was obvious when associated with a myelomeningocele (Case 5). The spina bifida involving the entire lumbar region could be palpated in Case 3. An abnormal bony protrusion was associated with the palpable spina bifida. Although defects in fusion of the vertebral neural arch were present in all the cases, they could not be detected on clinical examination in 3 instances.

Neurologic disturbances were present in 3 and absent in 2 cases. Case 1 was hospitalized because of fever of unknown origin and generalized weakness. Neurologic examination was essentially normal. However, the thoracic hypertrichosis suggested an underlying vertebral defect which could have been associated with her febrile disease and required further roentgenologic examination. In the other case, neurologic examination was also within normal limits but the child had been born with a dorsolumbar hypertrichosis and a right clubfoot, both of which signs prompted a search for an underlying vertebral anomaly.

The more common neurologic disturbances were characterized by impaired function of one or both lower extremities. The parents of the patients usually noticed either difficulty in walking or in learning to walk. Weakness and paresis of the flexors or extensors of the foot and toes, unilaterally or bilaterally, associated with diminished or absent patellar or Achilles reflexes and sensory disturbances, are not infrequent. Often the affected extremity is slightly smaller than normal. The complications of infection, ulceration, and necrosis of a toe or part of a foot may develop in an area of anesthesia unknown to the patient or his parents (Case 2). Sphincteric impairment was present only in the case presenting the myelomeningocele. This child also had a severe paraparesis with analgesia of both lower extremities and hydrocephalus.

Lumbar puncture does not offer much help in making a diagnosis. Since there is ordinarily no obstruction to the circulation of spinal fluid, the manometric and spinal fluid findings are usually entirely normal.

Roentgenologic diagnosis. Roentgenologic examination of the entire spine in anteroposterior and lateral positions is important in the investigation of neurologic disorders involving the lower extremities or the sphincters and in the presence of congenital cutaneous defects over the spine. Most cases present a spina bifida occulta, commonly in the lumbar region, which may be associated with a fusiform widening of the spinal canal at the site of the spina bifida or cephalad to it. The characteristic bony spicule, producing a line of increased density in the center of the spinal canal and reported by many investigators, is not necessarily present. Such a shadow is not seen if the cord-dividing septum is cartilaginous or fibrous in nature. A bony spur arising from the posterior portion of the vertebral bodies was observed in the roentgenograms of 2 of our patients (Cases 1 and 4). This bony spur may be attached to the fused or open neural arch. Other roentgenologic anomalies seen were partial or complete fusion of the involved vertebral bodies, wedged vertebrae and hemivertebrae, fusion of adjacent laminae or spinous processes, and narrowing of intervertebral disc spaces. Other spinal and rib anomalies may also be encountered. The reported cases presented spina bifida and fusiform widening of the spinal canal with increase in interpedicular distance.

Visualization of the anomaly by pantopaque myelography should be done in all cases. It localizes accurately the level of the lesion. The anomaly is demonstrated by a splitting of the opaque column into two columns passing around a fusiform central defect produced by the bony, cartilaginous, or fibrous septum. This split in the pantopaque column was usually longer and wider than the visualized bony spur. A unilateral filling defect at the site of the bony changes caused by nonfilling of the subarachnoid space around one part of the divided cord as reported by Cowie (5) has not been seen in this series. Myelography may also reveal

the presence of a neoplasm, such as a lipoma or dermoid, associated with this type of myelodysplasia.

Babies and unco-operative children may need a short general anesthetic for myelography. An aseptic meningitis complicated this test in 1 case.

Treatment. According to various reports and our own observations, the spinal cords of some of these patients did not change their position relatively to the vertebral column as normally occurs. The upper portion of the conus medullaris was visualized at the fifth lumbar vertebral level at the age of 6 months in Case 3. It is known that at the age of 3 months of intrauterine life the spinal cord segments correspond anatomically to the vertebral segments. At birth the lower end of the spinal cord lies at the third lumbar vertebral level and in adult life at the first lumbar vertebral level. In the lumbar and inferior thoracic regions of the spinal cord, where most of the myelodysplasias and fixation of the cord occur, the relative "upward migration" of the spinal cord becomes impossible, and one may assume that it produces considerable tension on the spinal cord and may result in increasing neurologic disturbances during the period of bony growth. The early release of the lesion fixing the spinal cord low in the spinal canal by removal of the bony, cartilaginous, or fibrous septum should allow normal spinal cord development and prevent the increase in neurologic dysfunction. Thus the purpose of operation is prophylactic rather than curative.

The operative treatment consists in the removal of the cord-transfixing elements and mobilization of the spinal cord. This is done through a laminectomy approach. The extradural removal of the septum should always be attempted; however, such may be possible only by an intradural approach and necessitate section of one or two nerve roots. Resection of the dura surrounding the transfixing septum together with the usually present adhesions between it and the arachnoid and pia of the split halves of the cord is necessary for complete mobilization of the spinal cord.

Pathology. The division in the cord itself may extend for several segments cephalad as well as caudad to the abnormal septum while the dural cleft usually approximates the size of the bony spur or the cartilaginous or fibrous septum. An entirely fibrous septum was encountered in Cases 2 and 5. In Case 3 a bony septum transfixed the cord to the left of the midline and was so large that it could be palpated through the skin. The septum in Case 4 was bony, cartilaginous, and fibrous. In Case 1 the septum transfixing the cord was entirely fibrous while the bony spicule arising from the floor of the spinal canal only penetrated the spinal cord anteriorly to a depth of about 5 millimeters. The cleft in the spinal cord lay in its center in 3 cases, and in Cases 3 and 5 the spinal cord was asymmetrically divided, one half being larger than the other. When the cord was divided in symmetrical halves, the ipsilateral nerve roots arose from each portion. In Case 3 the posterior roots arose from each respective half of the split cord while the anterior roots arose entirely from the larger of the two halves and passed above and below the central septum and anterior to the smaller half of the cord to meet with the posterior roots.

Since none of these patients died, there has been no opportunity to examine histologically the abnormal neural structures. Such studies on myelodysplasias of various types have been reported in the literature, and I wish to refer to the studies of von Recklinghausen, Wieting, Bruce, M'Donald, and Pirie (2, 3), Zalewska-Ploska, Kino, Weil and Matthews, Lichtenstein, Benstead, and others. They report multiple distortions of the spinal cord structures but no actual duplication.

It is believed that the embryologic defect producing diastematomyelia occurs during the fourth week of gestation during the formation of the neural tube from the medullary plate. According to the experimental work of Speman, Needham, and others, as

brought out by Campbell and others, the mesenchyme derived from the mesoderm of the supporting somites has the prime function of inducing neural tube formation in addition to supporting and insulating it. Thus the various types of myelodysplasias may result from faulty mesenchymal induction which could be secondary to environmental abnormalities interfering with the direction of the morphogenetic movement. The various components of the vertebral column including the notochord and the dura arise from the primitive mesenchyme. Observations and experimental work on amphibia and birds have suggested that aberrant factors such as high temperatures have created reactions which led to abnormal neural ectodermal induction. Similar adverse influences may be responsible for spinal dysraphism in man.

Results. Follow-up examinations of these patients were carried out at regular intervals for periods of 8 months (Case 5) to 2½ years (Case 1). The first 4 patients have shown some clinical improvement. Two are asymptomatic while 2 others (Cases 2 and 3) still show a slight difference in size between their two lower extremities. Case 2 shows loss of motion of the toes on the left and analgesia of the corresponding leg and foot. The baby with the thoracic myelomeningocele developed a severe postoperative pseudomonas infection of the cerebrospinal fluid pathways from which she recovered. However, her hydrocephalus continued to increase. Following her recovery from meningitis, she exhibited a severe paraparesis with analgesia of both lower extremities.

SUMMARY

Five verified cases of diastematomyelia are reported. All cases presented various types of cutaneous defects such as hypertrichosis, dermal sinus, or defective skin. One was associated with a thoracic myelomeningocele and another with a lipoma. The neurologic disorders consisted of: (1) weakness in one or both lower extremities producing disturbances of gait and stance, (2) underdevelopment of one lower extremity associated with (3) sensory loss and ulceration in the anesthetic area of the foot and toes, (4) reflex changes, and (5) impaired function of the vesical and rectal sphincters.

The preoperative roentgenologic findings were characteristic and showed spina bifida with fusiform widening of the spinal canal and the occasional presence of a density corresponding to a midline bony spicule arising from the anterior portion of the canal and extending into the canal. Myelography regularly outlined a midline septum which divided the subarachnoid space in two columns, usually over several segments.

Treatment consisted of exposure of the defect through a laminectomy, removal of the midline fibrous, cartilaginous, or bony septum which split the spinal cord into two distinct structures, and mobilization of the split spinal cord. The patients have either improved clinically or failed to show progression in their neurologic disorders.

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AGENESIS OF THE SACRUM

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SINGLE CASES of sacral agenesis have been reported from time to time in the literature, and Freedman was able to find 44 such records, adding 1 of his own. Our own experience leads us to believe that the condition is rather more common than Freedman's figures would suggest, and a review of a series of personally investigated cases revealed several points of interest. It soon became clear that we should have to treat as separate groups the cases of a short sacrum associated with rectal and anal deformities and those in which the bowel was normally formed although it might be functionally disturbed. In the latter group neurologic disturbances have been the chief feature of the symptomatology, while in the former the visceral nerve supply seemed often to be intact and the shortening of the sacrum was apparently not always due to true agenesis.

SACRAL AGENESIS WITHOUT ANORECTAL ANOMALIES

Eight patients exhibiting various degrees of true sacral agenesis have been available for study. All of these have been referred for examination on account of urinary symptoms and have proved to have a neurogenic disorder of bladder function. The 8 patients have as their common factor a complete absence of the lower sacral and coccygeal elements; no case of simple absence of the coccyx has been included and the full number of lumbar vertebrae has been demonstrated in all. There has, however, been some variation in the exact nature of the bony deformity.

In 3 cases, only 1 sacral vertebra was present, and that was poorly developed with a divided or partially divided body (Fig. 1); as a result the iliac bones were more closely approximated posteriorly than normal. Despite the apparently limited area of sacroiliac contact in these 3 cases, there has been very little evidence of instability of the pelvic ring, and the gait has been good.

In 2 the sacral agenesis has been associated with a complex malformation of the fourth and fifth lumbar vertebrae causing some scoliosis (Fig. 2). In these the sacrum has been represented by not more than two segments, though exact interpretation of the x-ray film is difficult.

In the remaining 3 cases there have been 3 sacral segments present, and no bony deformity has been evident except for a slight laminal defect of the fifth lumbar vertebra (Fig. 3).

Neuropathology. All the cases were in children, all of whom had had symptoms from birth or from the age at which their parents first concerned themselves with the child's urinary control. The fact that there has been no instance of a late onset of symptoms is remarkable, since in other sacral deformities without meningocele which have been studied there has often been no evidence of nerve involvement until adolescence or adult life. For example, 4 patients have been examined whose sacrum, though complete in its number of segments, has been reduced in size and twisted into a curious "scoliotic" position: in these 4, urinary symptoms were first noticed at the ages of 10, 14, 40, and 54 years. Similar histories were noted in some cases of sacral spina bifida occulta. Only 1 patient with sacral agenesis has come to postmortem, a girl dying at the age of 12 years, having a complex malformation of the lumbosacral junction and rather more extensive neurologic signs than the others. We are indebted to Dr. R. Pugh, Pathologist of St. Peter's and St. Paul's Hospitals, for the following report:

From The Hospital for Sick Children, Great Ormond Street, London.

FIG. 1. Sacral agenesis: sacrum represented by only 1 complete vertebra, hemivertebra above. Girl aged 3 years with neurogenic bladder.

FIG. 2. Sacral agenesis with complex malformation of the lower lumbar vertebrae. Boy aged 10 years with neurogenic bladder.

The cervical and upper thoracic portions of the cord were softer than usual and were flattened from before backward and, on palpation, there was an obvious and quite severe degree of hydromyelia present. The right half of the cord appeared larger and also slightly softer than the left half. At the level of the eighth thoracic segment the cord divided into two distinct portions, a smaller left component and a larger right component which ran on down together for a short distance and then diverged slightly and carried on downward as two separate structures. At a point 3.5 centimeters below the division of the cord the two components were separated from each other by a rounded bar of fibrous almost cartilaginous tissue, 2 centimeters long and 0.3 centimeters in diameter, which ran from before backward horizontally across the spinal canal, dividing it into two portions. There was, thus, a form of diastematomyelia present. The left component of the cord was a rounded filamentous structure, 0.5 centimeters in diameter at its upper end and 0.35 centimeters in diameter at its lower end. It was of firm consistency and no central canal was obvious on palpation or could be found on cross section. Several small rudimentary nerve roots emerged from the left side of this portion of cord, but none was seen emerging from the right side. The right component was a flattened oval structure, 1.3 by 0.3 centimeter in its maximum diameters at the upper end, and 0.8 by 0.2 centimeter at the lower end. It was of extremely soft consistency and its central canal, which was continuous above with the central canal of the cervical and upper thoracic portions of the cord, was obviously very considerably dilated. Normal sized nerve roots emerged from its lateral margin. Each component ended in a cauda equina at the level of the upper part of the second lumbar vertebra.

Although the other patients probably did not suffer from such extensive lesions, it seems likely that in all of them a myelodysplasia was present, rather than a specific interference with a few spinal roots.

Clinical features. The bony deficiency produces curiously little external deformity when coincident abnormalities of the lower lumbar spine are present. There may be flattening of the gluteal region and poor development of the natal cleft, but these are features which may well be overlooked on superficial examination. As in cases of spina bifida, a dimple is sometimes present in the

FIG. 3. Sacral agenesis. Lateral view showing a sacrum represented by 3 vertebrae. Boy aged 4 years with neurogenic bladder.

sacral region, and in 1 case there was a fibrofatty pad of tissue. Palpation of the sacral area will at once betray the defect in the more advanced cases, though it is not easy to differentiate clinically the cases of agenesis from those of "sacral scoliosis." When only the lower segments are missing, palpation with a finger in the rectum is essential for clinical diagnosis.

Minor abnormalities of the feet have required orthopedic attention in 5 cases of this series, and 1 patient has a severe paralysis of 1 leg with dislocation of the hip. Freedman found several examples of the latter deformity in his collected series and attributed it to the abnormal position of the os innominatum consequent upon sacral deficiency; it seems more likely to be a paralytic phenomenon, however, since it commonly accompanies all types of congenital spinal cord lesion.

In spina bifida occulta and in spina bifida cystica causing only partial interference with the cord and nerve roots, it is often observed that deformities of the legs and feet are present without any evidence of disturbance of the nerve supply to the bladder or bowels; while the contrary state, urinary incontinence without limb deformity is rare. When the bony lesion is purely sacral, it might be anticipated that the bladder would seldom escape and in fact no case of true sacral agenesis, involving more than one segment, without bladder disorder has been seen by us or found in a search of the recent records at The Hospital for Sick Children. The cases collected by Freedman on the whole support this finding, and only those 2 recorded by Pouzet appear to have been without doubt free from urinary trouble.

Severe constipation with absence of the normal sense of rectal distention has been the most common abnormality of the bowel and was present in 7 of the 10 patients. Constipation of this type represents the minimum disturbance of the innervation, and has been present without incontinence, but incontinence due to overflow with a relaxed anus was a feature of several cases at some time during the period of observation. As in other spinal cord lesions, a functional continence of feces may be achieved in the absence of proper nervous control. The anus in these children was seldom completely without tone, often it was closed at rest but took a long time to regain the closed position after digital dilatation. Some elements of the puborectalis sling were usually to be felt.

In traumatic and in most congenital spinal cord lesions anesthesia of the perineum is a constant concomitant of the neurogenic bladder, since the same nerve roots are involved, and use is often made of this observation in differentiating the neurologic disturbance from other causes of urinary retention or incontinence. In this series, however, normal perineal sensation was present in 4 cases. This feature is not peculiar to sacral agenesis and has been observed in other purely sacral lesions, such as spina bifida cystica, spina bifida occulta, and sacral scoliosis.

The type of bladder disturbance varied considerably from case to case and seemed

to bear no relation to the type of bony deformity. As with the rectum, it is possible for some continence to be attained, even in the presence of a severe neurologic disturbance: One child has a trabeculated bladder with free reflux into grossly dilated ureters and a funnel-neck deformity, yet is now able to keep herself dry by regular manual expression of urine. By contrast, there were 2 cases in this series in which urethral resistance was minimal, so that urine dribbled away continuously from an empty bladder and the ureters suffered no back-pressure effects. Thus in 1 instance a continent child has severe renal damage, in another a hopeless incontinence is associated with an entirely normal upper urinary tract. The urologic findings in these cases could be paralleled in other congenital spinal cord lesions, and a full discussion of them would be out of place in this report.

SACRAL AGENESIS WITH ANORECTAL ANOMALY

We were able to find 41 cases of imperforate anus and rectum in the records of the past 5 years in which the roentgenograms, although not made for the purpose, demonstrated the structure of the sacrum and lumbar spine. The films have been examined with Dr. B. C. H. Ward of the Department of Radiology. Films of 25 babies with unrelated conditions have also been studied as controls.

Sacralization of a vertebra involves the development of several special features which may not all occur together. The level of the lumbosacral angle was taken as marking the beginning of the sacrum in this study because it is established before birth, as Keith (3) has shown, and can be identified on roentgenograms of the newborn as well as in older children. It is of course usually easy to recognize the upper limit of the sacrum in the anteroposterior film by other criteria such as the presence of lateral masses, the variation in the width of the intervertebral spaces, and the level of the sacroiliac articulations, but these points may not be clear in roentgenograms taken soon after birth. The roentgenograms were sufficiently extensive to allow of the vertebrae being counted from the first thoracic in 13 and from the first cervical in 15, confirming the relative rarity of abnormalities, other than rib variations, above the lumbar region. Coccygeal vertebrae were visible in some but are not included in the discussion or the chart because their development is not always roentgenologically demonstrable at birth.

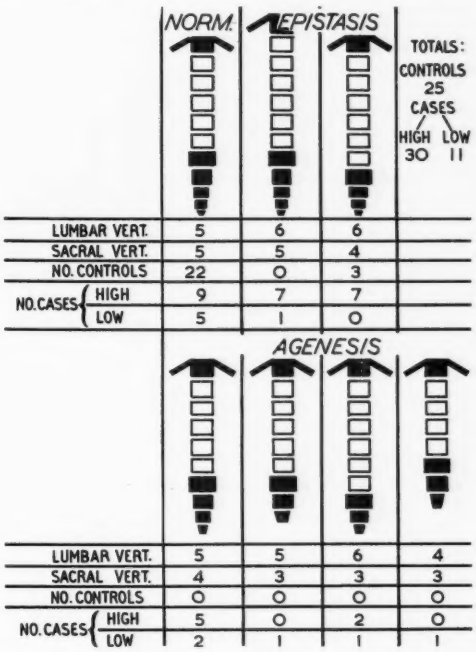

FIG. 4. Vertebrae present in controls and cases of high and low anorectal anomaly.

The anorectal malformations were grouped as high or low. In the former the bowel ended above the pelvic floor, with or without a fistulous opening ("imperforate rectum"). In the latter the bowel passed through the pelvic floor but no normal anus was present although some form of abnormal opening was common ("imperforate anus").

Figure 4 summarizes the main findings. In almost all the control cases the expected 5 lumbar and 5 sacral vertebrae were present. Three of the 25 patients, however, had only 4 vertebrae in the sacrum but had an

extra "sixth" lumbar vertebra to make up the usual 10 vertebrae between the thorax and coccyx. This arrangement (failure of specialization of the twenty-fifth or usual first sacral vertebra) was observed in 5 per cent of white human spines by Keith (4) and is normal in early orthograde primates. The condition was called "epistasis" by Gadow.

There were 11 children with low anomalies, almost half of them had a normal spine with 5 lumbar and 5 sacral segments, but in as many cases true sacral agenesis was present with suppression of segments.

Thirty high anomalies were examined. It will be seen that about a third had a normal spine but that most of the others showed epistasis. True agenesis of the sacrum with suppression of segments was only half as common. The frequency of epistasis is in keeping with the long backs and small buttocks that these babies often have.

It should be noted that the results of this study probably indicate an unduly high proportion of abnormalities in the low cases because many straightforward cases of "ectopic" and "covered" anus were treated without roentgenologic investigation though in almost all "high" cases roentgenograms were taken to assess the level of the end of the gut.

Bladder function is difficult to assess accurately in the newborn period, and perineal surgery may itself disturb this function by scar fixation of the bladder neck or even nerve damage. The assessment in this series is incomplete for this reason. It is significant that none of the patients with true sacral agenesis with only 3 sacral segments has yet been proved to have normal bladder function—in 3 it is definitely abnormal as in the cases of agenesis without anorectal abnormality described. However, of those with 4 sacral segments, 2 have definitely normal function and the younger ones have no symptoms as yet.

Many of the patients with epistasis have normal function although in 1 baby a trabeculated bladder was demonstrated before any pelvic surgery was carried out. Two others have proved deficiency of bladder function but the sacral segments, though present, were deformed.

Stephens stated that a sacrum with 4 parts would probably be associated with normal development of the pelvic floor whereas a shorter one would often be associated with incomplete formation of the levator ani. This observation correlates with our findings. The former would include short sacrum due to epistasis or agenesis of 1 segment, and the latter only true sacral agenesis with suppression of more segments.

The practical conclusion to be drawn from this study is that a sacral deformity or true sacral agenesis with loss of more than 1 segment is likely to be associated with bladder dysfunction; but that epistasis, which is a commoner finding in association with imperforate rectum, can often occur with normal bladder function.

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A CORRELATIVE STUDY OF PERIPHERAL CORONARY PRESSURES AND CORONARY ARTERIOGRAPHY FOLLOWING CORONARY OCCLUSION

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SINCE FIRST DESCRIBED by Lower in 1669 the intercoronary circulation has been the subject of extensive clinical, anatomic, and functional investigation.

Studies of human and animal hearts by various methods have led to diverse interpretations and conclusions relative to the existence and function of intercoronary communications. Accordingly, it was believed that the correlation of an in vivo anatomic and functional study would be of interest and value in clarifying the subject.

Furthermore, since the function of the extracoronary circulation naturally occurring or surgically produced may vary depending on the functional state of the intercoronary circulation, it seemed necessary to study the changes in peripheral coronary pressures before, during, and after coronary occlusion. The study was undertaken to evaluate the time, rate, and magnitude of the development of the intercoronary circulation by means of peripheral coronary pressure determinations and by coronary arteriography done before and at varying intervals following coronary artery ligation.

Following the concept of radiographic demonstration of vascular structures by Moniz and Dos Santos, Rousthöi was the first to visualize the coronary arteries in the living animal, rabbits, dogs, and monkeys. Others have subsequently reported coronary arteriography in living animals. Human studies first reported by Radner in 1945 have had additional clinical trials. The interested reader is referred to the comprehensive report of Di Guglielmo.

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MATERIALS AND METHODS

Unselected mongrel dogs ranging between 2 and 23 kilograms were anesthetized with intravenous nembutal (veterinarian), 30.8 milligrams per kilogram of body weight. Animals were intubated and the endotracheal tube was connected to a mechanical respirator. Thoracotomies for acute coronary artery ligation and for peripheral coronary pressure studies were done through the left fourth or fifth interspaces. The pericardium was incised anterior to the phrenic nerve and retracted. The left coronary artery was identified and all principal branches, the septal, left anterior descending, and circumflex were identified before ligation which was done distal to the septal artery in all instances. In performing peripheral coronary pressure determinations a 19 to 21 gauge needle attached to a polyethylene catheter was directed into a major branch of the left anterior descending branch of the left coronary artery, connected to a Statham strain gauge (P23A), and readings were taken on a Sanborn polyviso recorder. Continuous pressure tracings were made before, during, and after acute coronary artery ligation. Animals surviving acute ligation in this and allied study groups were

TABLE I.—PERIPHERAL CORONARY PRESSURES FOLLOWING ACUTE LIGATION L. A. D.*

Dog No.	Pulm. art. pressure	Aortic pressure	Control P.C.P.†	P.C.P. mm. Hg and related time intervals following occlusion: 5 sec.	30 sec.	1 min.	2 min.	3 min.	4 min.	5 min.	6 min.	7 min.	8 min.	9 min.	10 min.	Result
650	—	86/75	94/86	15/11			15/10		8/6			13/10			19/16	D 4 hours
641	12/8	86/83	68/64	15/11		10/8	10/8	8/7	5/4	3/3	3/3	3/2	2/2	2/2	2/1	V.F. 16 min.
655	8/6	75/71	94/92	18/18	3/3	9/8	10/9	8/7	7/6	7/6	7/6	7/6				V.F. 7 min.
658	7/2	124/120	139/135	9/9		7/6	5/5	11/11			6/5		13/13	13/13	11/11	D 24 hours
642	8/5	86/82	98/94	3/3	3/3	15/8	13/8	10/6							14/12	Survival
648	—	95/87	113/106	3/3		3/2	1/1	1/1	.75/.7	1/1	3/3	13/8	7/4			V.F. 9 min.
657	8/3	94/90	130/120	15/11	4/3	6/6	6/6	7/4	7/4	8/6	8/6	8/6	8/6	9/8	9/8	D 24 hours
659	11/8	101/98	101/94	7/6		8/7	10/9	10/9		24/9	24/9	21/10	21/10	21/10	21/10	Died surgery 24 hours
667	26/15	130/122	126/102	7/3	1/.75	1/.7	1/.7									V.F. 2 min.
665	20/8	109/102	102/95	7/3	14/12	16/12	16/12	9/8	4/0							V.F. 4 min.
819	29/15	153/131	124/109	34/28	26/17	26/19	15/14	9/8	4/3	2/2	3/2	3/2	2/2	2/2	2/2	V.F. 10½ min.
817	26/9	131/112	83/71	38/19	6/5	4/3	2/1	2/1	3/2	2/1	2/2	4/3	6/5	6/5	2/2	V.F. 10½ min.

*L.A.D., Left anterior descending branch.
†P.C.P., Peripheral coronary pressure.
V.F., Ventricular fibrillation.
D, Died.

TABLE II.—PERIPHERAL CORONARY PRESSURES DISTAL TO OCCLUDED SITES

Dog No.	Date of ligation of L.A.D.*	Days interval to study of P.C.P.†	Aortic pres., mm. Hg	P.C.P. circumflex, mm. Hg	P.C.P. L.A.D., mm. Hg	Visualization of ligated L.A.D. by coronary arteriography
659	9-14-55	1	112/105		4/0	—
653	9-6-55	6		82/78	60/52	+
653	9-6-55	13	78/75	75/71	58/41	+
642	8-24-55	20	60/56	56/54	52/50	+
647	8-24-55	21	78/75	67/56	67/56	—(technical error)
622	8-3-55	37	82/78	48/45	52/48	+(26 days)
595‡	8-29-55	44	90/79	86/83	83/68	+
598‡	8-29-55	44	71/64	71/48	64/60	+
620‖	9-1-55	50	83/79	83/71	94/90	+
602‖	8-29-55	50	71/64	90/75	90/83	+
604‖	8-29-55	50	45/41	75/60	56/49	+
614‖	8-31-55	50	86/83	94/79	94/90	+
634	8-15-55	64	34/25	42/34	42/34	—§
630	8-11-55	66	124/120	75/71	60/56	—(technical error)
568	7-20-55	82	71/64	68/64	71/68	+
563	6-20-55	112	94/83	86/71	83/56	—

*L.A.D., Left anterior descending branch.
†P.C.P., Peripheral coronary pressure.
‡Previous cardiopneumopexy.
‖Previous cardiopneumopexy with segmental resection followed by ligation of left anterior descending branch.
§Sensitivity reaction to dye. Cardiac arrest under fluoroscopy. Resuscitation. P.C.P. taken after resuscitation.

subjects for peripheral coronary pressure determinations at varying time intervals. Chronic peripheral coronary pressure studies were immediately preceded by coronary arteriography.

Coronary arteriography was done by the transcarotid route at various intervals following coronary artery ligation. A small incision was made in the right paratracheal region. The carotid artery was isolated and ligated distally. A polyethylene catheter containing a radiopaque ureteral stilet was inserted into the carotid artery proximal to ligation and directed centrally. A loose ligature was placed around the artery and catheter centrally to prevent bleeding. Positioning of the catheter at the base of the aorta was done under fluoroscopic control. Small doses of contrast media (urokon 70 per cent), 2 to 3 cubic centimeters, were used to confirm the position of the catheter.

Three exposures were made in each subject using 4 to 10 cubic centimeters of contrast media with each exposure (32 centimeters tube distance, 1/60 second exposure, 360 M.A., 50 to 65 K.V.). As will be seen by the results the timing of the exposure with the injection is important.

RESULTS

Peripheral coronary pressure changes following acute occlusion. In 12 consecutive studies, continuous peripheral coronary pressure tracings were made for 10 to 16 minutes following acute coronary ligation. The peripheral coronary artery pressures in all instances fell to 8 millimeters of mercury or less (Table I). These low pressures recorded following acute ligation are more representative of mean pressures than systolic and diastolic as charted. In most the fall of peripheral coronary pressure was progressive, terminating in ventricular fibrillation. Only 1 of this group survived beyond 24 hours. This high mortality (91.7 per cent) was greater than that obtained in control ligations of the same artery, closed and open chest experiments, in a subsequent series of 78 dogs (55 per cent). In several studies there was a rise of peripheral coronary pressure following the abrupt fall, the maximum reading obtained being 24/9 millimeters of mercury (dog 659). This animal died during a surgical procedure on the first postoperative day.

Peripheral coronary pressure changes following chronic occlusion of coronary arteries. In 16 experiments (Table II) in animals surviving acute coronary artery occlusion there was a progressive development of the intercoronary collateral circulation until approximately 3 weeks at which time the peripheral coronary artery pressure of the previously occluded vessel (left anterior descending branch) approached, equaled, or exceeded that of the measured unoccluded vessel (circumflex branch). It will be noted that the systemic pressures in these animals with 2 exceptions were considerably lower than those obtained in the preceding experiments. Two possible explanations come to mind. First, coronary arteriography was done immediately preceding thoracotomy and study of peripheral coronary pressures. A possible toxic factor related to the injection mass is suggested since mortality was encountered with this procedure. Secondly, the mechanism described by Murray may have been operative, namely, that coronary artery occlusion with myocardial infarction is accompanied by incomplete emptying of the ventricle and paradoxic movement of the infarct area. This results in diminished cardiac output, lower blood pressure, diminished coronary pressures, and all the clinical effects known in severe human coronary disease. All animals in this chronic study group had developed severe myocardial infarcts of the left ventricle, confirmed by autopsy. Both factors may have been operative.

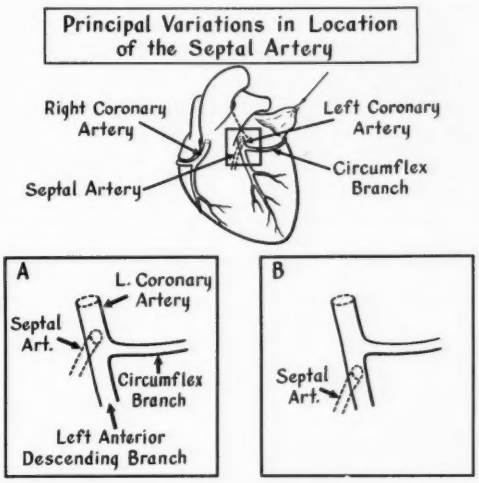

FIG. 1. Schematic drawing of main coronary arteries and branches (dog).

Results of coronary arteriography. A schematic drawing of the coronary arteries (Fig. 1) is included as a guide for the arteriograms.

The results obtained in the study of coronary arteriography in normal dog hearts and following acute and chronic occlusion are portrayed in Figures 2, 3, 4, 5, 6, 7, and 8.

DISCUSSION AND CONCLUSIONS

Following acute ligation of a coronary artery in the dog, peripheral coronary pressures of the occluded vessel fall precipitously to levels of 8 millimeters of mercury or less.

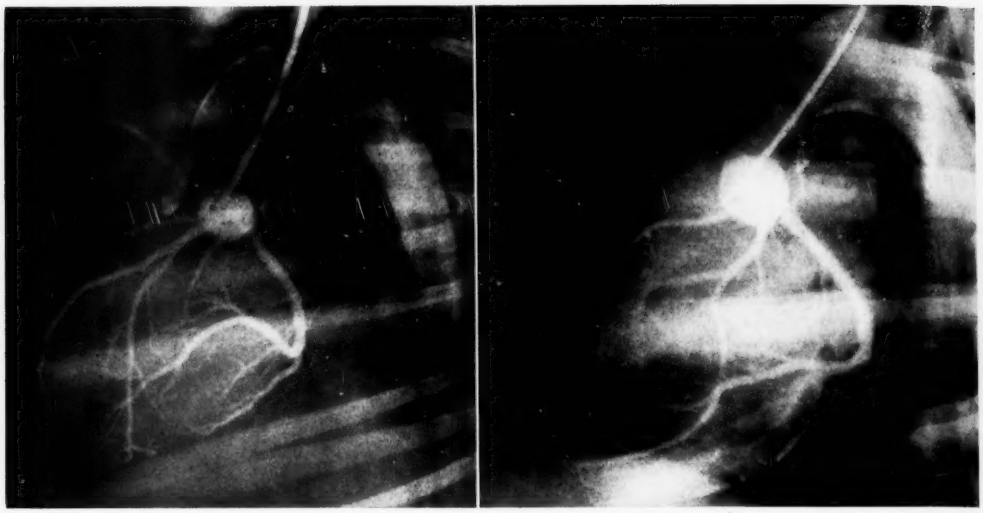

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FIG. 2.

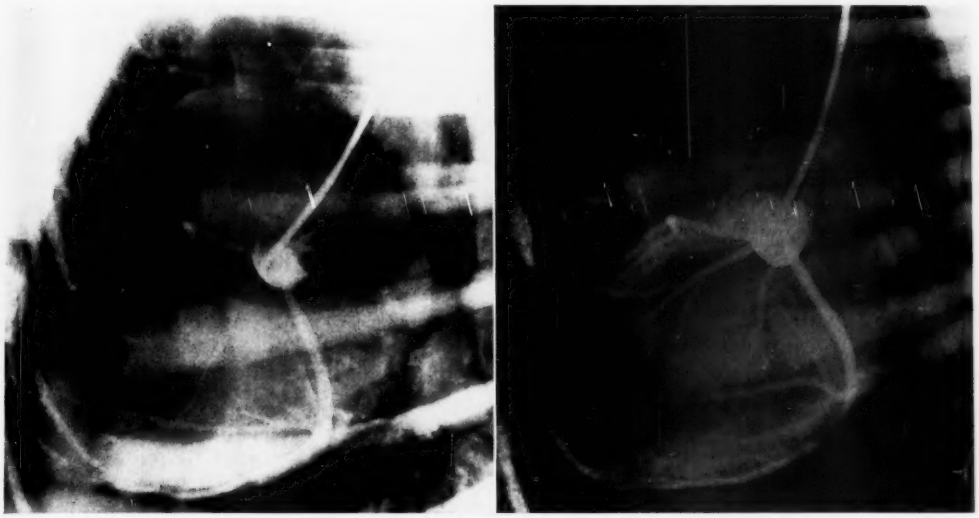
FIG. 3.

FIG. 4.

FIG. 2. a, Normal control coronary arteriogram (623) showing the right coronary artery and the left coronary artery with the principal branches, the septal, left anterior descending, and circumflex. b, Normal control coronary arteriogram (693). The principal branches of the left coronary artery, the septal, left anterior descending, and the circumflex are demonstrated. The right coronary artery is not visualized.

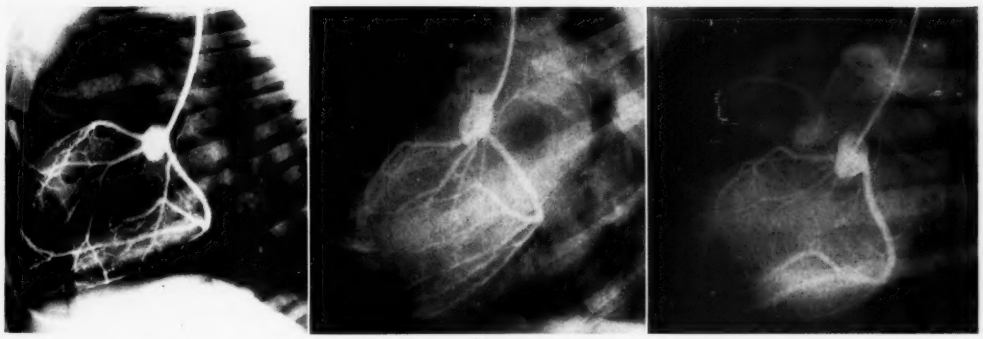
FIG. 3. Coronary arteriogram 30 minutes after acute ligation of left anterior descending branch which fails to fill in the contrast study.

FIG. 4. Coronary arteriogram (653) 6 days after ligation of left anterior descending branch, which is nevertheless visualized although attenuated contrasted to the normal septal and circumflex branches. Peripheral coronary pressure in the ligated vessel had not returned to normal (Table II).



a b

FIG. 5.



a b c

FIG. 6.

FIG. 5. a, Coronary arteriogram (642) 20 days following ligation of the left anterior descending branch. Incomplete filling of the ligated vessel is noted. b, A different exposure of the same subject shows complete filling of the ligated vessel in which peripheral coronary pressure was approaching normal (Table II). The timing factor of injection and exposure is obviously important.

FIG. 6. a, b, and c, Coronary arteriograms 622, 604, and 614 done 26, 50, and 59 days respectively following ligation of the left anterior descending branch of the left coronary artery. Note: (1) visualization of the previously ligated artery and (2) increase in the intercoronary communications. Peripheral pressures had returned to normal in 622 and 614 (Table II).

These low levels may be sustained, may rise slightly, or fall progressively indicating that the function of already existing intercoronaries is limited. The initial readings immediately after coronary artery ligation are appreciably lower and at variance with those reported by Gregg, Thornton, and Mautz and Eckstein and Leighninger who reported initial readings immediately after occlusion in the range of 30/20 millimeters of mercury. An explanation for this difference is not immediately apparent. Possibilities are the measuring apparatus and technical aspects reported by these authors

FIG. 7. Coronary arteriogram (563) 112 days following ligation of left anterior descending branch. Only the left circumflex artery is visualized even though the peripheral coronary pressure in the ligated vessel was essentially equal to that of the circumflex artery (Table II). Different timing of exposure and injection of the contrast media would probably have shown filling of the previously occluded artery. This is due to the phasic filling of occluded arteries (83).

such as the control of systemic pressure at approximately 100 millimeters of mercury by adjustable clamps around the aorta and the infusion of blood and solutions.

Gregg gave no explanation for the different results. Possible factors may be (1) the method for determining the true zero, (2) intermittent occlusion of the needle in the coronary artery during the cardiac cycle, (3) air bubbles in the recording system, and (4) systemic blood pressure which may modify coronary artery pressures. None of these factors was overlooked in the peripheral coronary pressure determinations. It is possible that in this particular group of 12 consecutive dog studies, not selected survivors, the intercoronary circulation was minimally developed. This fact could account for the low peripheral coronary pressures obtained following coronary artery ligation and also the high mortality in this group (91.7 per cent). Once again the variations in the consequences of coronary artery ligation are emphasized. Simultaneous recording of systemic pressure with peripheral coronary pressure following ligation may have helped to delineate the significance of a constant systemic pressure as was maintained in the experiments of Gregg, Thornton, and Mautz and Eckstein and Leighninger.

Immediately (30 minutes) following coronary artery ligation, coronary arteriography failed to demonstrate the occluded vessel. This method of demonstrating intercoronaries, though simpler, would appear to be less sensitive than the methods of Prinzmetal using fluorescein and radioactive erythrocytes.

At various intervals (1 to 112 days) following acute coronary artery ligation in surviving dogs determinations of peripheral coronary pressures in the previously ligated vessel (left anterior descending branch) show that this modality acquires a magnitude equal to that of an unligated coronary artery (circumflex) in approximately 3 weeks. These data are in agreement with former allied studies by Mautz and Gregg. The development of the intercoronary circulation as demonstrated by coronary arteriography paralleled the rise of peripheral coronary pressures in the occluded coronary artery. The left anterior descending branch was first demonstrated by arteriography 6 days (Fig. 4) following ligation. It is possible that this phenomenon could be demonstrated at earlier dates although studies at such intervals were lacking.

The practical significance of these findings may be applied to the following:

1. The production of apparently normal arteriograms in the presence of occluded arteries suggests limitations of the method as a means of clinical diagnosis. Additional experience and variations in pathology such as segmental occlusions may negate this feature. The need for multiple projections with rapidly changing cassettes is borne out by the sequential rather than simultaneous filling of intercoronary arteries and obstructed arteries. Pressure curves of Gregg

(7) support the phasic filling of occluded coronary arteries.

2. Attempts to produce a physiologic need in terms of reduced pressure gradients by chronic progressive occlusion of a major coronary artery branch would appear doomed to failure inasmuch as the intercoronary circulation expands and peripheral coronary pressures distal to occlusion return to levels similar to those of unoccluded vessels. It is likely that the same phenomenon would occur following chronic occlusion of the main coronary artery. It is probable that even though peripheral coronary pressures return to normal following chronic occlusion, the total coronary reserve is reduced. This perhaps may be elicited by increasing cardiac work load.

3. The development of the intercoronary circulation following chronic coronary artery occlusion would suggest that extracoronary sources of blood, if governed principally by pressure gradients rather than metabolites or nerve action, function variably depending on the functional state of existing intercoronaries.

4. The unmitigating manner in which the intercoronary circulation develops following chronic coronary artery occlusion casts doubt upon the validity of dependency tests as tests of revascularizing procedures since the coronary and intercoronary circulation may be adequate without blood from extracoronary sources. Further, it is possible that since pressure gradients are abolished the development of the intercoronary circulation may be a limiting factor to the long-continued function of an extracoronary source of blood of a systemic nature. This may not apply for a graft of a lower pressure system such as the lung which usually presents a pressure gradient relative to the normal or obstructed coronary arteries.

5. The expansion of the intercoronary circulation as noted in this study and as previously reported requires emphasis and denotes an inseparable and reciprocal relation to an extracoronary blood source, naturally occurring or surgically produced.

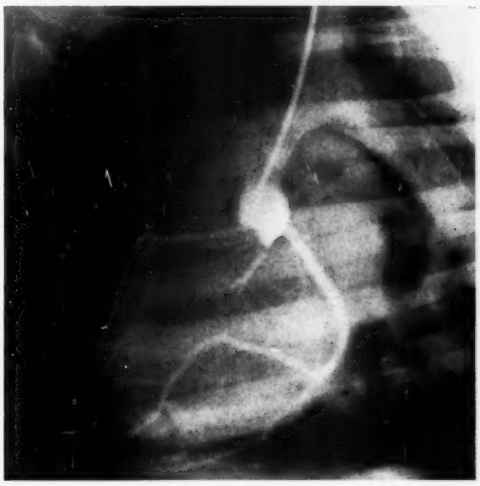


FIG. 8. Coronary arteriogram (620) 50 days after ligation of the left anterior descending branch. Partial filling of the ligated vessel is noted although the peripheral coronary pressure of the ligated vessel was normal (Table II).

6. The fall in peripheral coronary pressure following acute coronary occlusion offers a pathophysiologic basis for directional blood flow from an extracoronary source to the coronary bed (5).

SUMMARY

1. Peripheral coronary pressure determinations were made before, during, and after acute coronary artery ligation.

2. The low pressure readings obtained suggest a marked limitation of existing functional intercoronary arteries.

3. Peripheral coronary pressure determinations in chronically occluded coronary arteries show that this modality returns to levels of unoccluded neighboring arteries in approximately 3 weeks.

4. The findings by coronary arteriography done at varying times following coronary artery ligation paralleled the peripheral coronary pressure readings.

5. The significance of these findings is discussed as applied to: clinical coronary arteriography, attempts to establish a physiologic need by chronic occlusion, the validity of dependency tests, and the reciprocal

relationship between coronary and extracoronary blood sources.

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NUCLEAR STRUCTURE IN CANCER TISSUES

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OUR LABORATORY has been engaged in an attempt to identify the unique structural features of cancer tissues and their regional lymph nodes which define or are correlated with the survival of cancer patients. Previously it had been found that prolonged survivals in breast and gastric cancers were associated with nuclear differentiation and lymphoid infiltration in the primary tumors and sinus histiocytosis of the regional lymph nodes (1–5).

The present study represents an extended and more detailed evaluation of nuclear structure in human cancer tissues. An attempt was made to answer the following questions: What is the extent of nuclear variability among cancer cases? What is the relation between nuclear structure and survival? Does the nuclear structure of cancer tissue remain constant?

MATERIAL AND METHODS

An examination was made of the microscopic structure of 1,829 primary cancers representing 42 different cancer types. The tumors were mostly from the surgical pathology files of the Flower and Fifth Avenue Hospitals and the sections had been prepared by routine formalin fixation and hematoxylin and eosin staining. The nuclear structures were classified from 0 to 4 according to their degree of differentiation in a manner previously described. Nuclei showing a high degree of similarity, no chromatin clumping or condensation, and absent or minimal nucleoli were assigned a nuclear grade of 3 or 4. In contrast, anisonucleosis, chromatin clumping prominent nucleoli, and mitotic figures were taken as criteria of nuclear anaplasia and graded 0 or 1. These latter features are characteristically representative of the cytologic criteria of malignancy. Intermediate degrees of nuclear chromatism and nucleolar prominence were assigned a grade of 2.

An evaluation was made of the relative frequency of the various nuclear grades within the different cancer types and in the entire series. Of the total series, 392 patients were known to have survived a minimum of 5 years postoperatively while 310 patients died of the disease within 6 months of diagnosis. These two subgroups were utilized to obtain information regarding the relationship between survival and nuclear structure. In addition, an examination was made of the microscopic structure of 142 recurrent cancers in which the original biopsy was available for comparison.

RESULTS

Table I presents the per cent incidence of the various degrees of nuclear differentiation found among different cancer types as well as in the total series. It is clear that the nuclei of cancer cells did not invariably exhibit the criteria of malignancy. In the total series only 58 per cent of the patients had truly anaplastic nuclei (N grades 0 and 1). In 28 per cent, the nuclear structure had a moderate degree of differentiation (N grade 2), while a high degree of nuclear differentiation was found in 14 per cent of the series (N grades 3 and 4).

Well differentiated nuclei were found in an appreciable percentage of the cancers of the thyroid, breast, bladder, and prostate. However, all of the cancer types examined had examples of tumor tissues composed of well differentiated cells lacking nuclear anaplasia. Such cases could not have been identified as cancer on the basis of their cytologic features alone.

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This study was aided by a grant from the Ray and Charles Newman Foundation.

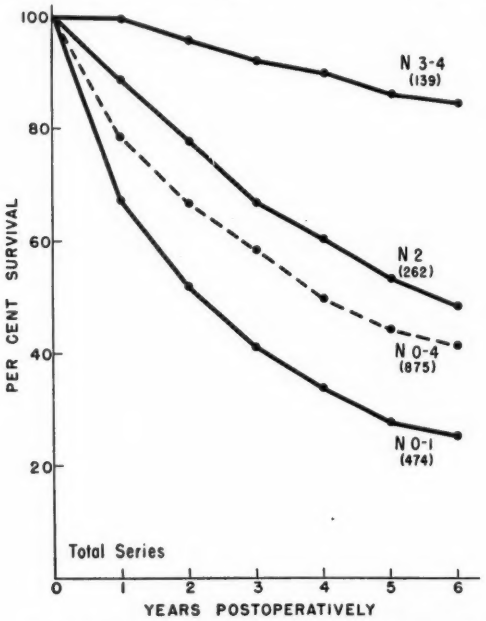

FIG. 1. Per cent postoperative survival of patients with cancers of diverse types in relation to their degree of nuclear differentiation.

Of the cases studied, 392 patients were known to have survived a minimum of 5 years after the original biopsy and treatment. The distribution of nuclear grades within this group is indicated in Table II. It should be noted that these cases included diverse types of cancer. The incidence of highly anaplastic nuclei among these cases was less than was encountered in the total series, viz., 34 per cent as compared to 58 per cent respectively. Conversely, the incidence of highly differentiated nuclei was greater than in the total series; 31 per cent as compared to 14 per cent respectively. Thus, cancers having a better than average survival were characterized by a higher degree of nuclear differentiation and a lower frequency of anaplastic nuclei than the general population of cancer cases.

TABLE I.—NUCLEAR GRADE IN HUMAN CANCER TISSUE

Tumor type	*No.*	*N grade, per cent* 0–1	2	3–4
All cases	1829	58	28	14
Bladder	42	62	21	17
Breast, female	869	49	30	20
Cervix uteri	45	71	27	2
Colon	310	60	31	9
Lung	70	93	6	1
Ovary	44	61	30	9
Prostate	27	71	22	7
Stomach	160	65	30	5
Fundus uteri	34	42	51	9

Of the total series, 186 patients were known to have died of their disease within 1 year of the time of biopsy and initial treatment. These cases plus cancer tissues obtained from 124 autopsies were evaluated as to their nuclear structure. This combined group represented more than 30 different cancer types. The data obtained are presented in Table II. The nuclear structure of this group was characterized by a virtual absence of highly differentiated nuclei. The low incidence of differentiated nuclei in this series as compared to the total series and the long survival series suggested that nuclear anaplasia was associated with a poor prognosis.

The correlation between N grade and survival was studied in the total series and in various subgroups. Figure 1 presents the survival curves obtained in reference to nuclear grade but without regard to cancer type, curability, or other structural features of possible prognostic significance. Despite the diversity of cancer types in each of the nuclear grades there was a definite correlation between N grade and survival. The time for 50 per cent of the different nuclear populations to die (LT 50) was found to be 2.2 and 5.8 years for N grades 0–1 and 2 respectively. Of the N grade 3–4 group, only 15 per cent were dead 6 years postoperatively.

The analogous curves obtained upon separate analysis of colon and breast cancer cases are presented in Figures 2 and 3. These data also show differences in the survival curves in relation to the N grade. It will be noted, however, that the survivals were apparently much greater in the breast series as compared to the analogous N grade curves in the colon series. Figure 4 presents the N grade survival curves for breast cancer

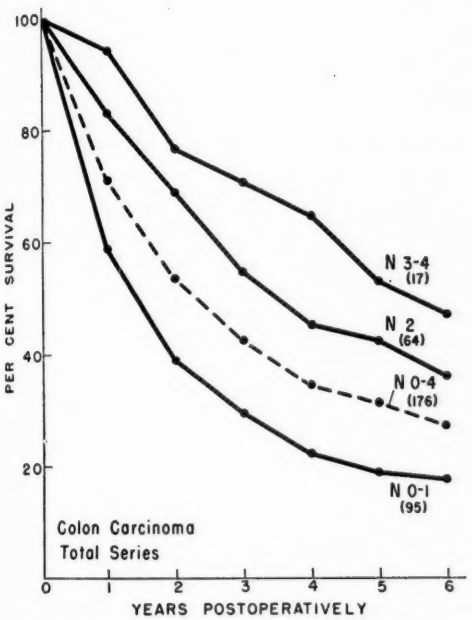

FIG. 2. Per cent postoperative survival of patients with colon carcinomas in relation to their degree of nuclear differentiation.

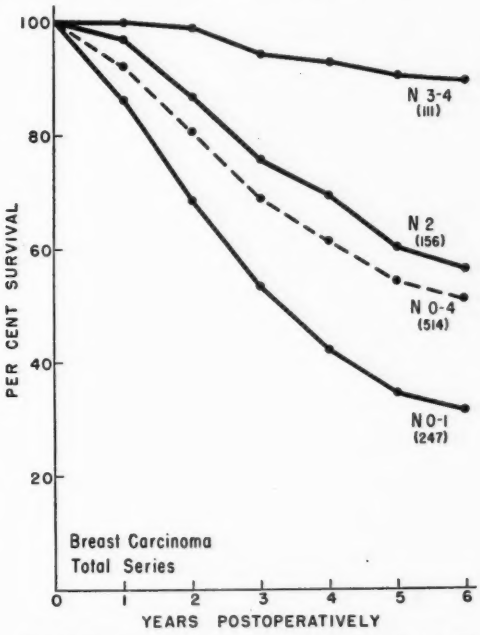

FIG. 3. Per cent postoperative survival of patients with breast carcinomas in relation to their degree of nuclear differentiation.

patients lacking sinus histiocytosis of their regional lymph nodes and lymphoid infiltrate of the primary tumor. These data provide a more adequate control to the colon cancer series since such prognostically significant structural features are rarely observed in colon cancers. The resulting survival curves are now seen to be more similar to those of the colon.

In order to remove the influence of curative therapy on the N grade survival relationship, we constructed the analogous curves for those patients known to have died of their disease. The data obtained are indicated in Figures 5 and 6. It is evident that a relationship between N grade and survival still persisted in both the colon and breast cancer series. However, the slopes of the survival curves in the breast series (Fig. 6) were not markedly different from those in Figure 4. In contrast, the curves in the colon cancer cases had a far more rapid fall (Fig. 5 as compared to Fig. 2).

The stepwise progression of the N grade 3–4 curve and the similar but less marked feature in the N grade 2 curve as contrasted to the straightness of the N grade 0–1 curve suggested that there might be a loss of nuclear differentiation with time. This was also suggested by the infrequency of well differentiated nuclei in autopsy material and among patients dying within 1 year after biopsy. In order to test this possibility a comparison was made of the nuclear structure in primary and recurrent lesions. Does the nuclear structure of cancer tissues remain constant?

In 88 cases repeat biopsies or autopsy material were available for comparison with the original tissue specimen. In some cases

TABLE II.—PER CENT INCIDENCE OF NUCLEAR GRADES IN RELATION TO SURVIVAL

Series	*No.*	*N grade, per cent*		
		0–1	*2*	*3–4*
All cases	1829	58	28	14
Dead—1 yr.	310	85	15	1
Living—5 yrs.	392	34	36	31

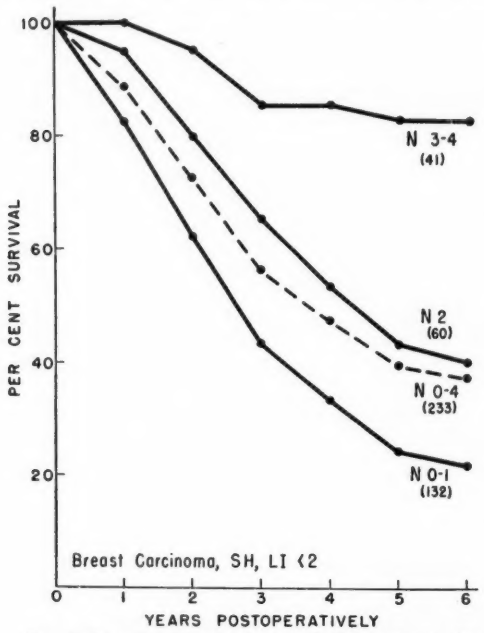

FIG. 4. Per cent postoperative survival of patients with breast carcinomas, lacking lymphoid infiltration in the primary tumor and sinus histiocytosis of their axillary nodes, in relation to their degree of nuclear differentiation.

more than 1 recurrence was obtained. In Table III we have indicated the changes in nuclear grade encountered in the recurrent cancer tissues. The various data may be considered according to the nuclear structure of the original biopsy.

Recurrent tumor tissues were studied from 12 cases of diverse cancers having well differentiated nuclei in the primary tumors. The recurrences represented biopsy and autopsy material and were obtained from several months to 17 years after the original biopsies. In 4 cases, more than 1 recurrence was available for study yielding a total of 19 recurrent lesions.

TABLE III.—CHANGES IN NUCLEAR GRADE IN RECURRENT LESIONS

Primary tumor	*No.*	*N grade in recurrence*		
		0–1	*2*	*3–4*
N grade				
3–4	18	9	5	4
2	25	17	7	1
0–1	99	92	7	—

In 8 of the 12 cases the nuclear structure of the recurrences was found to be anaplastic. These changes from the original nuclear structure occurred from 1 to 15 years after the original biopsy. In 3 additional instances the recurrent tumors had nuclear grades of 2. Table III presents the details of the nuclear grades as found in the recurrent lesions. The tendency for progressive nuclear anaplasia is evident in these data. In no instance did a preterminal biopsy (6 months before death) or autopsy specimen fail to disclose a lower N grade than the primary tumor. It would seem that cancer patients having well differentiated nuclei died of their disease only after progressive anaplasia of their nuclei.

Recurrent lesions were available in 25 cases whose original N grade was 2. In 17 cases the nuclear grade of the recurrences was 0 or 1. These changes occurred within a few months to 7 years. Fifty per cent of the cases were found to have undergone such nuclear change within a period of 4 years. In only 1 instance was the recurrence found to be N grade 3.

Recurrent lesions were obtained in 41 cases whose original N grade was 0 or 1. In 4 cases the recurrences were graded as 2. In no instance was a recurrence graded as 3.

COMMENTS

The data obtained in this study permit some conclusions of general interest to the phenomenon of malignant neoplasia and provide at least partial answers to the questions which were posed at the beginning of the investigation.

Cancer tissues of diverse types were found to exhibit differences in their degree of nuclear differentiation. Such variations in nuclear differentiation were encountered in the vast majority of the different cancer types. It would thus appear that the cancerous transformation of tissues is not necessarily associated with the structural characteristics commonly referred to as the cytologic criteria of cancer.

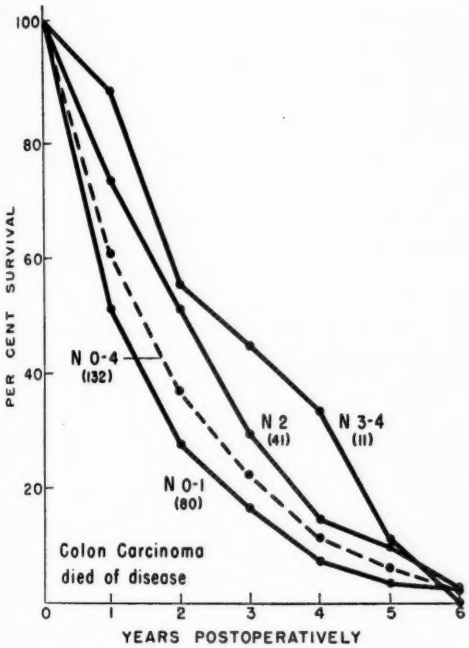

FIG. 5. Per cent postoperative survival of patients with colon carcinomas, known to have died of their disease, in relation to the degree of nuclear differentiation present.

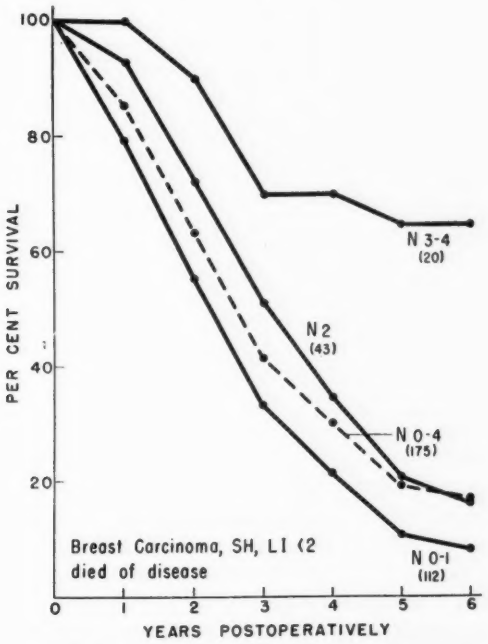

FIG. 6. Per cent postoperative survival with breast carcinomas. Lymphoid infiltration was lacking in the primary tumor and sinus histiocytosis, in the axillary lymph nodes, and patients known to have died of their disease.

The nuclei of cancer tissues obtained at autopsy or from those patients known to have died within 1 year after the original biopsy were predominantly anaplastic (85 per cent). Less than 1 per cent of them had well differentiated nuclei. In contrast, almost one-third of the patients known to have survived for 5 years or longer had highly differentiated nuclei. Thus, nuclear variability was less among those patients grouped according to their subsequent survival (Table II) then among the total series. These data confirm our previous observations on breast and gastric carcinomas and indicate the existence of a general relationship between nuclear structure and the lethality of cancer.

The relationship between N grade and survival (Figs. 1 through 7) demonstrated that the lethality of cancer is directly related to the nuclear structure. This relationship may be modified by, but is not dependent on, curability. It is noteworthy that in the colon cancer series a distinct flattening of the survival curves was found in the total series but not in the groups known to have died of their disease. In the breast cancer series such a difference between the total and the dead series was minimal. These data would suggest that curative therapy limited the lethality of the colon cancers whereas such an effect was not clearly demonstrable for the breast cancer cases.

In those patients known to have died of their disease the lethality (death rate) of the N grade 2 and N grade 3–4 series increased with time and approached that of the N grade 0–1 cases. This finding suggested that the increasing lethality might reflect progressive anaplasia of the differentiated nuclei, a possibility which was consistent with the infrequency of differentiated nuclei in preterminal and autopsy specimens. Direct

support for this suggestion was provided by a comparison of the nuclear structure in primary and recurrent lesions.

Since the origin of cancer or its ability to metastasize was not found to be dependent upon nuclear anaplasia, the essence of malignant neoplasia appears to be a more subtle cellular alteration than overt microscopic changes in the nuclei. This conclusion would be consistent with the hypothesis of Green which suggests that the essential change in cancer is a loss of "identity proteins" of the cell allowing for heterotopic compatability. However, the lethality of the disease does appear to be related to nuclear anaplasia.

The various data obtained in the present study would justify the following statements: (1) Individual cancer cases vary in their degree of nuclear differentiation. (2) Nuclear differentiation is not inconsistent with invasion and metastases. (3) The degree of nuclear differentiation of cancer tissues may be correlated with lethality as expressed by the survival curves, the per cent 5 year survival, and the LT 50 value. (4) This relationship is not dependent upon curability alone since it obtains in those patients subsequently dying of their disease. (5) In cancer patients dying of their disease the death rate is most uniform for the N grade 0–1 group whereas the death rate of patients with differentiated nuclei increases with time and approaches that in the N grade 0–1 cases. (6) Recurrent tumors tend to exhibit a progressive anaplasia of their nuclear structure. (7) The nuclear grade may be considered as a structural representation of the lethality of the tumor. (8) The present study has not indicated those factors responsible for the existence of different nuclear grades or the mechanism of increasing nuclear anaplasia.

SUMMARY

The nuclear structures of 1,829 primary cancers were studied and graded in terms of their degree of differentiation. Similar studies were also made of recurrent lesions and cancer tissues obtained at autopsy.

Survival curves were plotted in relation to the degree of nuclear differentiation (N grade). The data indicated that:

1. Individual cancer cases vary in their degree of nuclear differentiation.

2. Nuclear differentiation is not inconsistent with invasion and metastases.

3. The degree of nuclear differentiation of cancer tissues may be correlated with lethality as expressed by the survival curves, the per cent 5 year survival, and the LT 50 value.

4. This relationship is not dependent upon curability alone since it obtains in those patients subsequently dying of their disease.

5. In cancer patients dying of their disease the death rate is most uniform for the N grade 0–1 group whereas the death rate in cases with differentiated nuclei increases with time and approaches that of the N grade 0–1 cases.

6. Recurrent tumors tend to exhibit a progressive anaplasia of nuclear structure.

7. The nuclear grade may be considered as a structural representation of the lethality of the tumor.

8. The present study has not indicated those factors responsible for the existence of different nuclear grades or the mechanism of increasing nuclear anaplasia.

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PREVENTION OF EXPERIMENTAL PANCREATIC FAT NECROSIS

VI. Dextran

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WE HAVE DEVELOPED a simple method by which abdominal fat necrosis, usually fatal (3-5), is induced in the majority of dogs. The procedure consists of excision of the main pancreatic duct from the duodenum, together with a collar of duodenal mucosa; the duct is left open and the duodenum is closed. We have tried to prevent the development of this fat necrosis by the local application of various trypsin or lipase inhibitors, injections of diamox, banthine, antihistamines, and various other substances. Only intraperitoneal application of sodium formaldehyde sulfoxylate and of quinine (both of which are lipase inhibitors) had marked beneficial effects; both lowered the incidence of fat necrosis from 85 to 38.5 per cent and the mortality from 80 to 30 per cent. These results could not be improved by various combinations of the drugs and were the best we were able to obtain (2, 6-9).

Recently, experiments have been performed in our laboratory (1) to study the effect on pancreatic secretion of various intravenous solutions and drugs used in the treatment of shock. This study was carried out in order to establish which of these substances stimulated pancreatic secretion and, therefore, should be avoided in acute pancreatitis, and which seemed recommendable for clinical use because of absence of stimulatory effects on the pancreas. The intravenous administration of dextran was found to produce a marked, long-lasting inhibition of pancreatic secretion stimulated by secretin. On the basis of this observation, we decided to try intravenous dextran for its effect in our experimental procedure. These experiments were performed as described previously (3-5) on 20 healthy mongrel dogs of either sex, weighing between 5 and 13 kilograms. For the first 3 postoperative days, the dogs received daily 100 milliliters of 6 per cent dextran solution[1] intravenously and, as in all previous experiments, antibiotics intramuscularly. Of the 20 dogs, 5 died with extensive fat necrosis, 4 on the second, and 1 on the sixth day after operation; 2 dogs, which were sacrificed on the fifth and sixth postoperative day respectively, showed a slight to moderate degree of abdominal fat necrosis. The remaining dogs were sacrificed after 6 to 8 days and showed no fat necrosis whatsoever.

Thus, in 20 dogs fat necrosis developed in 7 (35 per cent) and was fatal in 5 (25 per cent). This result is better than any previously attained. Though some of this effect of dextran may be due to plasma extension, it probably is attributable mainly to inhibition of pancreatic secretion. These favorable results call for the clinical trial of dextran in appropriate cases. Probably, its use will prove of value in cases in which the development of fat necrosis is threatening, as in pancreatic injuries and following operations on and near the pancreas (that is, pancreatic biopsies, removal of lesions of the pancreas, penetrating duodenal ulcer, and difficult closure of the duodenum in gastrectomy). It likewise should be of benefit in conditions in which

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[1] 6 per cent dextran in saline (gentran solution).

inhibition of pancreatic secretion is of primary importance, for example, in acute pancreatitis and possibly pancreatic fistulas.

SUMMARY

The intravenous administration of dextran reduces the morbidity of experimental fat necrosis from 85 to 38.5 per cent and the mortality from 80 to 30 per cent. Clinical trial of intravenous administration of dextran seems advisable in acute pancreatitis, in traumatic and surgical injuries of the pancreas, and in pancreatic fistulas.

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GRANTLEY TAYLOR, M.D.

Peggy's Cove

EDITORIALS

PAINFUL POSTOPERATIVE SCARS

JAMES C. WHITE, M.D., F.A.C.S., Boston, Massachusetts

MOST SURGEONS are not sufficiently aware of the relative frequency with which intensely disagreeable pain and hyperalgesia can follow routine operative incisions. This complication arises most frequently after operations on the extremities, particularly in the region of the wrist, elbow, and groin; occasionally on removal of bone grafts from the tibia and iliac crest. It may also follow operations on the kidney, inguinal herniorrhaphy, intercostal drainage for empyema, thoracotomies, and paravertebral sympathectomies.

When the surgeon injures a subcutaneous or intercostal nerve in making his incision or by forceful retraction, a neuroma-in-continuity or terminal end-bulb is produced. Usually this causes the patient no inconvenience beyond a narrow zone of hypesthesia or paresthesia which gradually fades. At times, however, the initial numbness or electrical tingling is replaced by a peculiarly disagreeable burning type of sensation distributed over the course of the injured nerve. It may occur in spontaneous outbursts, often worse in cold, damp weather. Cutaneous stimuli evoke intensely disagreeable sensations, which may be so severe that the patient cannot even tolerate contact with clothing or bed-sheets. Experience with veterans examined after the last war (soon to be published by the Veterans Administration under the editorship of Barnes Woodhall) has shown that a similar syndrome may follow partial injury or transection of any peripheral nerve, often developing in the course of imperfect regeneration after neurolysis or suture. A striking example was a professional tennis player who had suffered a gunshot wound of the tibial nerve and 5 years later was still unable to play or even to walk barefoot because of pain on pressure against the sole of his foot. Five hundred twenty-nine veterans out of a total 2,962 examined at various examining centers in the follow-up study of peripheral nerve injuries had complaints of hyperalgesia to a greater or lesser extent 3 to 7 years after neurolysis or suture.

The best explanation of this phenomenon has been given by Landau and Bishop.[1] They point out that pain is transmitted by two types of neurons, the rapidly conducting myelinated delta fiber and the slowly conducting unmyelinated C fiber. The former can be blocked selectively by pressure of a tourniquet and the latter by dilute procaine solution. Experimenting on themselves, they were able to show that, when the delta fibers are blocked, stimulation of the remaining C fibers gives rise to a peculiarly disagreeable burning sensation with a prolonged afterdischarge. It is therefore probable that in many partial injuries of nerves activation of the C fibers is the cause of persistent dysesthesia. After suture it is the patient with partial but poor sensory reinnervation that is likely to complain.

Few forms of chronic persistent pain present greater difficulties in treatment than

[1] LANDAU, W., and BISHOP, G. H. Pain from dermal, periosteal, and fascial endings and from inflammation; electrophysiological study employing differential nerve blocks. Arch. Neur. Psychiat., 1953, 69: 490-504.

these neuralgias that follow apparently trivial injuries to unimportant nerves in the course of routine surgical procedures. Occasionally excision of a neuroma-in-continuity with suture of the nerve has been successful when this has been followed by good sensory regeneration. Simple resection of an end-bulb is rarely of any use, even when special steps are taken to prevent the formation of another neuroma. One man, who had suffered incapacitating dysesthesia in the sensory distribution of his superficial radial nerve after an operation on the radial head, insisted on a forearm amputation. Despite advice to the contrary he had this done elsewhere, only to develop even more disagreeable sensations in a phantom hand.

In cases of severe persistent intercostal neuralgia following thoracotomy or drainage of empyema, and also in painful hernia scars, we have tried posterior rhizotomy. Even the wide band of anesthesia produced by cutting 4 sensory spinal roots has not always been successful. On the other hand, anterolateral cordotomy can be relied upon to give complete relief in 4 out of 5 cases in which the neuralgia involves the trunk or lower extremities. It cannot be counted on to ensure lasting analgesia of the upper extremity. The failures result when the patient is still able to differentiate rapid pricks of a pin from simple tapping with a blunt object. This is likely to occur in 1 patient out of every 5 after high thoracic cordotomy for pain below the umbilicus, even though the cordotomy is performed by an expert. Ultimate failure is considerably more frequent when the operation has to be done in the upper cervical spine in attempts to relieve painful incisions in the upper half of the thorax or arm. The reason for this is inherent in the difficulties in severing all the fibers in the spinal pain pathway and its anatomic variations, as recently shown by White, Richardson, and Sweet.[2] Lasting difficulties with bladder emptying, weakness of the leg on the side of the incision, or disagreeable paresthesias in the analgesic area are rare complications, amounting to less than 5 per cent after a unilateral cordotomy. Despite the difficulties with this procedure, we have been forced to use it as a last resort in a series of 8 cases of truncal and lower extremity pain. Satisfactory relief was obtained in 6 patients who have been followed for periods up to 8 years. For similar cases of neuralgias in the upper extremity the results have been so uncertain that at the present time there does not appear to be any practical solution.

This experience in a large neurosurgical clinic, where we have been particularly interested in the problems of persistent pain, emphasizes the importance of avoiding trauma to nerves in routine surgery. This complication does not seem to occur in children. Also, in operating on the central portions of the thorax or abdomen, when there are no nerve trunks of any size, the surgeon need have no worries. On the other hand, in operations for hernia, on the kidney and ureter, paravertebral sympathectomies, and particularly in thoracotomies, he should take every precaution not to bruise, stretch, or cut an exposed nerve, or to include it in his closing suture. Before operating on an extremity the surgeon, even if well acquainted with the course of the larger trunks, will do well to look up the distribution of the smaller superficial nerves in a standard anatomic text and to plan his incision to avoid them. If a ramus is inadvertently cut, approximate its ends with 1 or 2 sutures of fine silk. The smaller fibers regenerate well and will rarely give rise to a troublesome neuroma if treated in this way. Some of the most troublesome chronic problems seen by the Hand Clinic at this hospital are due to lack of this precaution, especially in individuals with incisions on the dorsolateral surface of the wrist for carpal resection and de Quervain's disease in whom these precautions have been neglected.

[2]White, J. C., Richardson, E. P., Jr., and Sweet, W. H. Upper thoracic cordotomy for relief of pain; postmortem correlation of spinal incision with analgesic levels in 18 cases. Ann. Surg., 1956, 144: 407-420.

THE BILLROTH I GASTRECTOMY

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THE TURN IN THE TIDE of popularity against the Billroth I gastrectomy that we are currently witnessing comes as no surprise to students of the history of gastric surgery. When the resurgence of enthusiasm for this operation during the past few years is followed by a period of waning interest, the change is merely a fitting event in its lively and venturesome history. Ever since its first performance by Billroth, in 1881, the operation has been alternately praised and condemned. Billroth himself abandoned the method of restoring gastrointestinal continuity after gastrectomy by means of gastroduodenostomy as early as 1885 since he found the gastrojejunal restoration—which later came to be known as the Billroth II principle—a safer and technically easier procedure. The subsequent fate of the operation as a practical surgical modality was determined by the difficulty of uniting two structures of different caliber by end-to-end anastomosis. Kocher evaded the formation of the dangerous upper angle by closing the lower end of the sectioned stomach and by making a new opening in the posterior gastric wall which he anastomosed to the proximal end of the duodenum. But the other modifications suggested left unresolved the problem of "the angle of sorrows" until Shoemaker introduced his method of tubing the distal end of the stomach. The tube-like gastric remnant fashioned from the greater curvature of the stomach approximates the duodenum in caliber and permits suturing without tension. There still remained the problem of technical management in cases in which scarring and contraction of the first part of the duodenum are such that sufficient amount of duodenal tissue cannot be safely mobilized to permit end-to-end anastomosis. The modification worked out by von Haberer and Finney largely overcame this difficulty by closing the duodenum and anastomosing the distal end of the stomach to the second portion of the duodenum, the so-called terminolateral gastroduodenostomy.

Once these technical problems had been settled it became possible to use the Billroth I procedure in extended series of cases and to reassess its practical value in valid clinical terms. Leaving aside, for the moment, the analysis of clinical results, and confining one's attention to anatomic, physiologic, and clinical principles, the Billroth I operation offers a number of attractive features. Reestablishment of the normal anatomic relationship between the stomach and duodenum has the merit of similar restoration of continuity elsewhere in the gastrointestinal tract. The alleged physiologic advantage of having the gastric contents pass directly into the duodenum on the theoretic basis that the duodenum is better fitted to receive this acid secretion than the jejunum can be questioned, since the reason for the operation, namely, the presence of a duodenal ulcer, is evidence in itself that the duodenum is unable to cope with hyperacidity. One must bear in mind, however, that neither is there evidence that the jejunum is better able to withstand this secretion; in fact, all experimental data point to the contrary.

As regards technical considerations, the advantages appear clear-cut. For example, performance of the operation in the supracolic compartment of the abdomen minimizes contamination and simplifies the intervention when the use of local or block anesthesia is indicated. Moreover, the chief cause of mortality and morbidity after gastric resection, namely, the danger of leakage of the duodenal stump, is entirely eliminated when end-to-end gastroduodenal anastomosis is employed and is greatly reduced when the duodenum is closed as in the von Ha-

berer-Finney modification. In either instance there can be no back pressure in the duodenal lumen and thus one of the chief causes of duodenal disruption is eliminated. Likewise, the menace of closed loop obstruction —a not infrequent event after gastrojejunostomy owing to a kink in the proximal jejunal segment—is effectively warded off.

Nor are the advantages of the operation seriously compromised by the seeming technical shortcomings that have been cited from time to time. The objection that the Billroth I procedure is more difficult to perform, for instance, is correct only in the sense that any technique that is new to the operator presents technical problems. In point of fact, in experienced hands the Billroth I operation consumes less time than the Billroth II since the step of closing the duodenal stump is omitted. As regards the other commonly voiced objection, that in the Billroth I operation an insufficient amount of stomach is removed, it is not valid provided the principle of high ligation of the left gastric artery at its point of origin, as stressed by the late W. J. Mayo, is carried out and adequate mobilization of the duodenum is done. The painstaking performance of these requisite steps presents varying degrees of difficulty according to the anatomic and pathologic circumstances of the case. It must, therefore, be emphasized that all patients are not suitable for the Billroth I operation, and it may well be that enthusiasts in attempting to apply the procedure to all cases have brought undeserved discredit on the operation.

Attractive though these theoretic advantages appear, the true worth of the Billroth I operation—as that of any other surgical procedure—must be judged by its clinical results. In particular, to demonstrate the superiority of the Billroth I operation it is necessary to show that the mortality of the operation is no greater than that of the Billroth II, that the postoperative sequelae such as the dumping syndrome, failure to gain weight and resume full activity, and the like, are fewer than following the Billroth II procedure, and finally, that the incidence of recurrent ulceration is lower. A study of the statistical evidence in sizable comparable series of cases clearly indicates that there is little to choose between the two methods of operation as far as the rates of operative mortality and postoperative sequelae are concerned. The incidence of recurrent ulceration after the Billroth I operation is more difficult to assess since in most reported series sufficient time has not elapsed to enable the observer to formulate definite conclusions. It is, however, disconcerting to the proponents of the operation to find that the longer the follow-up observations the higher the recurrence rate. Projected into the future, this observation speaks ill for the Billroth I operation, as does also the finding recently reported that gastric acidity tends to remain higher after the Billroth I operation than after Billroth II operations of comparable radicalness. The latter observation, at the same time, supplies a hint of the reason for the differences between the results after the conventional Billroth I procedure and those after Billroth I operations supplemented by vagus section. In the latter the recurrence rate has been much lower than in the former, indeed at least as low as after conventional Billroth II procedures. As regards tractability, while the recurrent ulceration after both Billroth I and Billroth II operations is extragastric, the recurrent ulcer in the duodenum that follows the unsuccessful Billroth I procedure is more likely to respond to medical management than the jejunal ulcer that results from the failure of the Billroth II operation and thus will require reoperation less commonly. Of course, when surgical intervention becomes necessary, the technical problems presented by the recurrent duodenal ulcer are far more difficult.

What, then, is the position one may fairly assign to the Billroth I procedure in the management of duodenal ulcer? First of all, it seems that concerning the blanket condemnation of the procedure one's judgment —like the verdict of the Scottish jury—must

be "Not proven." As a primary technical method in the average patient, from the point of view of immediate results, there is little to choose between Billroth I and Billroth II procedures performed with comparable technical skill and care; strict adherence to technical details, however, is particularly important in the performance of the Billroth I type of operation. There is also good reason to suggest that the addition of vagus section to the conventional Billroth I operation significantly improves the incidence of recurrent ulceration. Finally, in some special situations such as the appearance of jejunal ulceration or severe dumping syndrome after a Billroth II operation, the conversion of the anastomosis to a Billroth I type often brings great benefit to the patient.

CARDIAC MONITOR FOR DETECTION AND DIFFERENTIATION OF CARDIAC STANDSTILL, VENTRICULAR FIBRILLATION, OR PERIPHERAL VASCULAR COLLAPSE DURING SURGERY

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ARCHER S. GORDON, M.D., Ph.D., Chicago, Illinois

THE MOST COMMON CAUSE OF DEATH in the operating room is cardiac arrest (cardiac standstill or ventricular fibrillation). Awareness of its danger and frequency has resulted in a standardization of treatment which is usually effective, if instituted early enough.

However, the extensive survey of Stephenson, Reid, and Hinton[1] reveals a relatively low incidence of permanent survival (28 per cent). This results from: (1) failure to recognize the condition immediately; or (2) delay in starting effective therapy. Cardiac resuscitation is usually successful if the proper diagnosis is made and adequate therapy is instituted within 4 minutes from the time of onset.

Most reported series are from large general hospitals with staffs well indoctrinated in the immediate treatment of cardiac standstill, ventricular fibrillation, and peripheral vascular collapse. Therefore, the most common cause for a poor outcome probably is failure to detect and differentiate these conditions early. Recognition of this fact led us to develop a small, portable, battery-operated cardiac monitor for the continuous, instantaneous, visual monitoring of the rate and rhythm of the heart.[2] In the anesthetized, pulseless patient, this instrument provides a means for the immediate detection and differentiation of cardiac standstill, ventricular fibrillation, or peripheral vascular collapse.

From the Department of Surgery, Veterans Administration Hospital, Hines, Illinois, and Department of Clinical Science, University of Illinois College of Medicine, Chicago.

[1] STEPHENSON, H. E., JR., REID, L. C., and HINTON, J. W. Some common denominators in 1200 cases of cardiac arrest. Ann. Surg., 1953, 137: 731-744.

DESCRIPTION OF CARDIAC MONITOR

The cardiac monitor (Fig. 1) has been described in detail elsewhere[3]. In addition to small size and portability, the use of a transistorized circuit makes it inexpensive and explosion-proof. Its self-contained power supply consists of two 1½ volt flashlight batteries.

The electrical activity of the heart is best detected by using subcutaneous needle electrodes, one near the right axilla and the other overlying the region of the cardiac apex. It is not mandatory for the needles to be placed in this optimum position. Satisfactory monitoring can be accomplished by placing needle electrodes between any two convenient locations on the right and left sides of the thorax, the right and left axilla, or even the right and left arms. The use of electrocardiographic plate electrodes on the skin represents a less effective method of attachment to the body. It may be used if de-

[2] Developed in collaboration with Radioisotope Unit, Veterans Administration Hospital, Hines, Illinois.

[3] FIELDS, T., KAPLAN, E., ABRAMS, B., SIMPSON, R., GORDON, A. S., and KENSKI, J. Cardiac monitor for surgery and resuscitation. J. Am. M. Ass., 1956, 162: 559-561.

sired, but skin resistance may seriously interfere with monitoring the optimal signal. If used, the skin must be thoroughly massaged with electrode jelly until an erythema is produced. When satisfactorily connected to needle or plate electrodes, the deflection of a galvanometer needle provides the continuous visual means of monitoring the electrical potential of the myocardium.

The frequency response of the unit is adequate for detection of tachycardias, bradycardias, extrasystoles, and other arrhythmias. For best monitoring of cardiac rate and rhythm, the galvanometer needle is adjusted so that the deflection represents only the major contraction of the ventricles. This is comparable to the QRS complex of an electrocardiogram. However, the cardiac monitor does not provide an electrocardiogram and is not intended to replace an electrocardiograph or oscilloscope. In the routine surgical case in which the use of such elaborate and expensive equipment is not practical or feasible, this device provides a constant monitor of cardiac activity.

An outlet is provided for optional use of a phone jack and earpiece by means of which the cardiac impulse can be monitored simultaneously from an auditory signal. This auditory signal is quiet and perceptible only to the one wearing the earpiece.

CLINICAL AND EXPERIMENTAL OBSERVATIONS

The cardiac monitor has been used on a large series of surgical patients undergoing major abdominal and thoracic procedures. At the operating table, it is usually suspended from an infusion stand near the patient's head where its response is continuously visible to the anesthetist and the surgical team. The electrodes are applied prior to the induction of anesthesia so that the pulse can be observed throughout the procedure. It has proved reliable and efficient in reflecting tachycardias, bradycardias, and extrasystoles, and has accurately detected cases of cardiac standstill, ventricular fibrillation, and peripheral vascular collapse.

The unit has also been useful for neurosurgical and ear, nose, and throat procedures. For pediatric use, especially in small infants, it is of assistance in following the patient's postoperative course as well.

Application of the cardiac monitor in emergency and admitting rooms has provided a useful means for assessing the initial status of critically ill patients and for carefully following their condition during treatment.

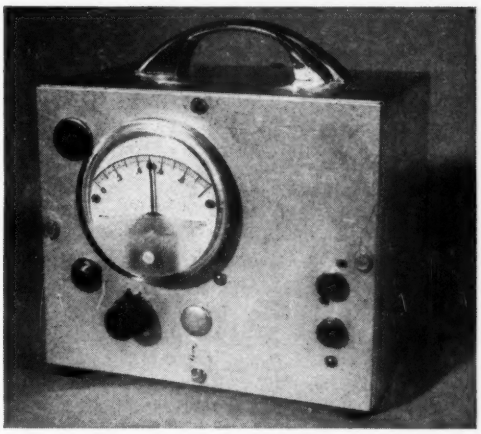

FIG. 1. Cardiac monitor.

Careful, controlled studies on dogs[4] have indicated that continuous monitoring allows immediate detection of cardiac standstill, ventricular fibrillation, and peripheral vascular collapse. These responses have been similar to those observed in human surgical cases.

Ventricular fibrillation was induced in a series of normal dogs by means of a rapid intravenous injection of 20 milligrams per kilogram of potassium chloride. Cardiac standstill was similarly produced in another series of animals with 50 milligrams per kilogram of potassium chloride. Peripheral vascular collapse was produced in dogs by the withdrawal of venous blood until the peripheral pulse became imperceptible.

Simultaneous recordings of femoral artery blood pressure and lead I electrocardiograms were made on a Sanborn poly viso, while the cardiac monitor was followed visually. For purposes of these studies, the output of the cardiac monitor was also recorded on the poly viso after passage through the phone jack and an impedance matching network (Figs. 2 to 5).

Normal response (Fig. 2). The normal heartbeat causes regular pulsations of the galvanometer needle. These are of constant amplitude, except for variations associated with respiration. This pulsation corresponds to the major wave of electrical activity of the ventricular myocardium.

[4]Animal studies supported by a grant from Chemical Corps Research & Development Command, Chemical Warfare Laboratories, Army Chemical Center, Maryland.

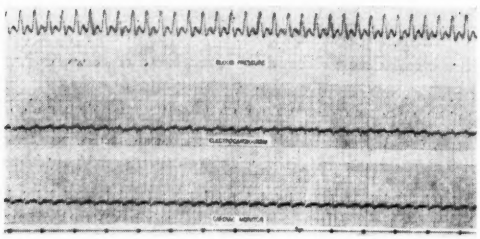

FIG. 2.

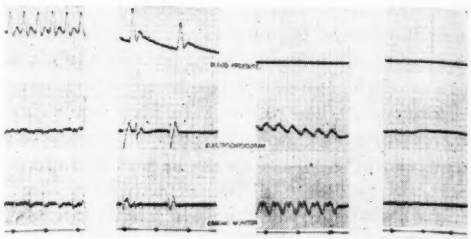

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 2. Recording of blood pressure, electrocardiogram, and cardiac monitor during normal sinus rhythm.

FIG. 3. Serial sections from recording of blood pressure, electrocardiogram, and cardiac monitor during progression from normal sinus rhythm through bradycardia and ventricular tachycardia into cardiac standstill.

FIG. 4. Serial sections from recording of blood pressure, electrocardiogram, and cardiac monitor during progression from normal sinus rhythm through bradycardia and ventricular tachycardia into ventricular fibrillation.

FIG. 5. Recording of blood pressure, electrocardiogram, and cardiac monitor during normotensive and severe hypotensive states showing minimal change in electrocardiogram and monitor tracings even when blood pressure has reached imperceptible levels during hemorrhagic shock.

Variations from the normal cardiac rate and rhythm are quickly and easily detected. Alterations in blood pressure, per se, do not significantly affect the amplitude or nature of the oscillations.

Cardiac standstill (Fig. 3). When cardiac standstill occurs, the movements of the galvanometer needle cease. This may be preceded by bradycardia or cardiac irregularities, which act as a warning of impending danger. Sudden cessation of needle deflections, with an absent pulse, indicates cardiac standstill if the electrodes are properly connected. The unit is so simple and electrically stable that, if it has been used for continuous monitoring of a patient's cardiac activity, loss of needle activity is presumptive evidence of cardiac standstill. When correlated with clinical findings, this becomes definitive evidence of arrest.

Ventricular fibrillation (Fig. 4). When the heart goes into ventricular fibrillation, it is usually preceded by aberrations of cardiac activity. These are reflected by the cardiac monitor. With the onset of ventricular fibrillation, the fascicular, asynchronous myocardial activity results in ineffectual cardiac output with loss of pulse and blood pressure. The needle of the cardiac monitor produces small, irregular, and highly erratic oscillations, completely lacking any regularity of rate or amplitude. The baseline (isoelectric line) shows a wandering throughout the range of the dial. The poly viso tracings from the cardiac monitor tend to duplicate the electrocardiographic pattern seen in ventricular fibrillation.

Peripheral vascular collapse (Fig. 5). During anesthesia, peripheral vascular collapse is more common than cardiac arrest. This condition results in dangerously low, frequently imperceptible, blood pressure and pulse, which may lead to an erroneous diagnosis of cardiac arrest and an unnecessary thoracotomy. However, even with

profound hypotension, the amplitude of deflections of the galvanometer needle on the cardiac monitor is not significantly reduced. The monitor hereby provides the crucial information in the pulseless patient that the heart is still beating. Proper and immediate therapeutic measures may then remedy the situation without resort to thoracotomy. Throughout this crisis, the anesthetist and surgical team are apprised of the patient's status on a beat to beat basis.

Arrhythmias and irregularities. Various irregularities and arrhythmias, such as auricular fibrillation, tachycardias, bradycardia, and extrasystole, can be identified by variations in rate and rhythm of the needle deflections. However, the device will not indicate such changes as S-T segment depression, auriculoventricular blocks, or differentiate between auricular or ventricular tachycardia.

COMMENT AND SUMMARY

The continuous use of a cardiac monitor at the operating table as an adjunct to careful clinical evaluation provides a means for detection and differential diagnosis of cardiac standstill, ventricular fibrillation, and peripheral vascular collapse. If survival rate is to be improved, it is imperative to prevent these conditions, if possible, and to detect them at once when they occur. It is important to differentiate them since the treatment for cardiac standstill and ventricular fibrillation varies significantly from that for peripheral vascular collapse.

Carefully monitored observations of irregularities of rate and rhythm may provide a warning that these serious conditions are impending. Constant attention is required since these irregularities frequently manifest themselves when the anesthetist is too busy to keep his finger on the pulse.

A practical cardiac monitor, which fulfills these needs, has been developed and tested. It consists of a small, simple, portable, inexpensive, explosion-proof, transistorized, battery-operated unit, which provides a continuous, instantaneous, visual pattern of the electrical activity of the heart.

Clinical observations and laboratory experiments have substantiated its effectiveness in: (1) monitoring the electrical activity of the heart on a beat to beat basis; (2) accurately reflecting cardiac activity during tachycardia, bradycardia, and arrhythmias; (3) immediately detecting the onset of cardiac arrest; and (4) differentiating ventricular fibrillation, cardiac standstill, and peripheral vascular collapse.

The Book Shelf

FRIEDRICH TRENDELENBURG AND THE TRENDELENBURG POSITION

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PROPER POSITIONING of the patient is essential for any operation. The *sine qua non* for pelvic laparotomy is the Trendelenburg position, which lowers the head and chest and elevates the hips, allowing the intestines to gravitate toward the diaphragm and thereby facilitating exposure of the pelvic viscera. The history of this inclined position dates back to antiquity. It has been described and its merits independently rediscovered probably more times than any other contribution to the annals of surgery. From the time of Celsus (ca. 40 B.C. to 20 A.D.) and for the next millennium the inclined position was used in the treatment of abdominal injuries, when eviscerated intestines had to be replaced within the peritoneal cavity. The position was described anew by Paul of Aegina (ca. 660 A.D.), and again by Abul-Kasim in the eleventh century.

In the ensuing years of the middle ages patients were placed in a semi-inverted position for both the manual reduction and surgical repair of abdominal hernias. The chapter on hernias in the famous manuscript of Roger and Roland succinctly describes this position and states its purpose: "In primis ergo patiens collocetur in banco, caput et humeros habens depressos, ut tota intestina descendant ad pectus, coxas vero et crura teneat elevata." This work, variously known as *Practica Chirurgiae* or *Post mundi fabricam*, the latter from the first 3 words of the preface, was probably written in the latter part of the twelfth century. Produced originally by Roger of Salerno, the manuscript was re-edited in 1252 by his pupil, Roland of Parma (1170 to 1264). Subsequent generations have identified it, the first Italian work on surgery, by the names of both Roger and Roland. Roger is also credited with being the first occidental to recognize the value of iodine, in the form of sea sponge ashes, in the treatment of goiter.

Among the several later authors who recommended an inclined position for the patient was Caspar Stromayr, a surgeon and ophthalmologist of Lindau am Bodensee. Stromayr's remarkable manuscript of 1559 deals largely with hernias. Profusely illustrated with color plates, each accompanied by a caption in old German verse, this manuscript provides both verbal and pictorial evidence (Figs. 2 and 3) of the author's use of the head-down position.

The inverted position was mentioned again in 1707, in a letter from Abraham Cyprian, a Dutch surgeon, to Thomas Millington. In reporting an operation for a case of advanced tubal pregnancy Cyprian wrote: "J'avois même pour plus grande precaution afin d'empecher que les boyaux ne descendissent, placé la malade en sorte que les parties superieures du corps étoient un peu abaissées, et la pauvre femme a même presque toujours demeuré dans cette même situation jusqu'a ce qu'elle a été tout afait guerie, pour éviter une hernie." At one time professor of surgery in

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Franeker, Cyprian later settled in London, where he reputedly performed 1,400 lithotomies in 12 years.

Percival Pott, in the middle of the eighteenth century, again pointed out the value of the inclined position in the reduction of hernias. "The posture of the body," wrote Pott, "and the disposition of the lower limbs, may be made very assistant in this operation, when the difficulty is considerable; the nearer the posture approaches to what is commonly called standing on the head the better, as it causes the whole packet of small intestines to hang, as it were, by the strangulated portion, and may thereby disengage it. . . ."

Elevation of the pelvis achieved gynecologic recognition in 1815 by Gutberlet, who suggested a pillow under the patient's hips as an aid to hysterectomy: "Man giebt nun der Kranken auf einem Tische oder erhöhten Bette eine horizontale Lage, bey welcher das Becken durch einen unterlegten Polster etwas erhöht wird; durch diese Lage schon wird bey der nachfolgenden Ausschneidung der Gebärmutter der Andrang der Gedärme in das Becken verhütet." More pronounced tilting of the patient's body was used by Freund in 1878, when he performed his celebrated total abdominal hysterectomy for uterine cancer.

Trendelenburg began to experiment with the inclined position in Rostock in 1880, for the repair of vesicovaginal fistula and other operations within the bladder. Four years later, in 1884, Trendelenburg's rediscovery of this surgical adjunct was reported by one of his assistants, Willy Meyer, who later migrated to the United States and achieved distinction on his own as one of the leading surgeons in New York City. Meyer's paper contains an interesting woodcut (Fig. 4) showing Trendelenburg's early method of maintaining the elevated pelvic position. An attendant, standing at the foot of and with his back to the operating table, supported the patient's flexed knees throughout the operation. In a later publication, in 1890, Trendelenburg compared this to the technique of the ancients in their treatment of hernia, but it is not clear whether he was aware of the centuries of previous experience when he first began to use the position, ten years earlier.

Meyer explained the Trendelenburg posture and its advantages as follows: "It is easy to understand how the viscera, because of their weight, fall back toward the diaphragm. The opened bladder gapes, just as the vagina in the lateral

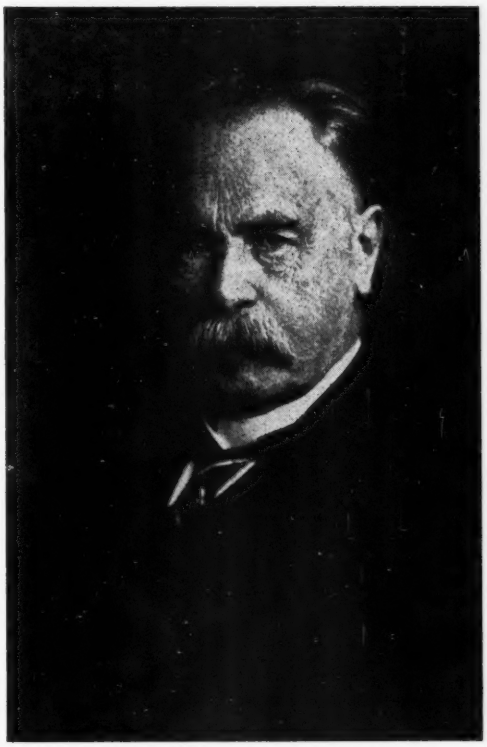

FIG. 1. Friedrich Trendelenburg (1844-1924).

Sims position, thus permitting not only a completely unobstructed view into its interior, but also, after retraction of the edges of the abdominal wall and bladder by means of broad, blunt retraction hooks, . . . the easiest introduction of the instruments necessary for extirpation and other manipulations. The vicinity of the trigone, which is the commonest site of bladder tumors, is thus also especially accessible to both observation and instrumentation. With the operating table placed as usual, and with its foot end opposite the window, the light then falls directly from the window onto the posterior inferior part of the bladder, thus illuminating not only the internal urethral orifice, but also very thoroughly the region of the ureteral orifices. Observations can thus be made that are impossible in the usual dorsal position. We could often see during our operations how the urine spurted in a little jet from the ureteral orifices, we could introduce sounds upward into the ureters and ascertain their accessibility and width, etc. Furthermore,

FIG. 2.

FIG. 3.

FIGS. 2 and 3. Illustrations from Caspar Stromayr's manuscript (9) of 1559, showing inclined position of patient for herniorrhaphy.

not to be minimized is the fact that the blood can now drain continuously toward the part of the bladder that is usually of less interest to us at this time . . . the operative field thus remaining relatively free of blood. In most cases this can not be achieved in the usual dorsal position. A lake of blood and urine tends to collect precisely here, at the trigone.

"No displacement of the organs nor any other disturbances at all result from the respiratory movements in this position, since the abdominal excursions are noticeable only up to about the midpoint between the umbilicus and symphysis. . . . How unusually free is the access then even to the deepest reaches of the posterior bladder wall. . . .

"This position is best designated as the 'elevated pelvic position.' "

Trendelenburg's personal comments on the elevated pelvic position, published in 1890 in association with his report of vesicovaginal fistulas repaired by the abdominal approach, stressed the value of this posture for delicate intravesical procedures. He wrote: "The elevated pelvic position has afforded us a means of operating under direct vision within the bladder with equal or greater ease than within the vagina. Thus nothing could be more natural than a transvesical attack on fistulas that cannot be managed successfully from the vagina. . . .

"If the patient is placed on the operating table so that the pubic symphysis forms the highest point of the trunk and the long axis of the latter forms an angle of at least 45 degrees with the horizontal, the abdominal organs . . . fall into the concavity of the diaphragm. The intestines fall out of the true pelvis as far as the atmospheric pressure will permit. In thin individuals with the rectus muscles relaxed under deep anesthesia, the anterior abdominal wall in the hypogastric

region exerts an actual sucking action on the pelvic cavity. . . .

"If a longitudinal or transverse incision is now made in the hypogastric region, as for lithotomy, and the rectus muscles and their posterior sheath are split, the air then enters the prevesical space at once, often with an audible sound. The peritoneum falls away and an extensive cavity is formed in the prevesical interstitial space, into which the light shines readily and in which the anterior wall of the bladder and the reflected fold of the peritoneum can be seen."

Trendelenburg quickly recognized the advantages of the elevated pelvic position for intraperitoneal as well as intravesical operations. "We work in the full light of the window," he enthused, "like the artist at his easel, without having to stoop . . . and without being burdened by protruding loops of bowel. . . . No one who has ever removed a myomatous uterus or an adherent ovarian cyst in this way will readily revert to the old procedure. The tumor falls out of the pelvis . . . as far as the intrapelvic connections permit. All the ligaments to be divided are put on a stretch and the blood drains away from the operative field. The intestines, which remain bunched together in the epigastrium, cause no concern as long as no vomiting occurs. . . .

"After the tumor is removed, a surprising view is obtained of the entire true and false pelves; the iliac and hypogastric vessels are seen pulsating, the course of the ureter is observed, and any small bleeding vessels can be picked up and ligated. . . . The elevated pelvic position is of great advantage in myomectomy, especially in difficult cases with intraligamentous extension of the tumor."

The improved exposure afforded by the position led Trendelenburg to recommend total hysterectomy in preference to the subtotal variety in cases requiring removal of the uterus. "The operation is made so easy," he wrote, "that panhysterectomy is carried out instead of supravaginal amputation. . . . This procedure, because of its safety and simplicity, surpasses the usual supravaginal hysterectomy. All steps of the operation can be carried out under visual control by use of the elevated pelvic position; blood loss is slight, and the elastic tourniquet for the uterus therefore unnecessary."

Utilizing Sims' discovery that when the pelvis is elevated the opened vagina aspirates air, Trendelenburg soon adapted his position for visualization of the vagina and rectum. "It is an excellent means," he explained, "of rendering the interior of the vagina or rectum accessible to the eye. Both cavities . . . gape widely as soon as their orifice is held open with the fingers, a short speculum, or some similar device. . . . With a manometer it can be demonstrated that the pressure in the lower abdominal cavity becomes negative when the elevated pelvic position is assumed. One need only connect a rubber tube to a catheter previously introduced into the bladder. Several experiments showed the pressure to be +1 cm. of water with the body in the horizontal position, while with the pelvis elevated the pressure fell to −6 to −8 cm."

FIG. 4. Woodcut from Willy Meyer's paper (6) of 1884, which first described Trendelenburg's use of the elevated pelvic position.

The term "Trendelenburg position" was first used in 1888 by Mendes de Leon, who reported his experience with this posture for a variety of pelvic laparotomies and for gynecologic examination of patients with tympanites. The name found immediate acceptance in a paper by Lange the following year and now enjoys universal recognition in surgical terminology.

Trendelenburg noticed facial edema in many of his patients maintained in a steeply inverted position, and soon obtained roentgenographic evidence of dilatation of the right side of the heart

355.

(Chirurgie No. 109.)

Über Blasenscheidenfisteloperationen und über Beckenhochlagerung bei Operationen in der Bauchhöhle.

Von

Friedrich Trendelenburg,

in Bonn.

Mit einer Lichtdrucktafel.

Seit ihrer Begründung durch Naegele, Dieffenbach und Jobert de Lamballe ist die Operation der Blasenscheidenfistel, besonders durch das operative Talent und die unermüdliche Ausdauer von Gustav Simon, zu einem so hohen Grad von Vollkommenheit gebracht worden, dass dieses Kapitel der gynäkologischen Chirurgie auf den ersten Blick fast vollständig abgeschlossen zu sein scheint. Neuere Vorschläge beziehen sich auf Modifikationen der Instrumente, der Lagerung und des Nahtmaterials, der Vorbereitung zur Operation und der Nachbehandlung; das Princip der Operation bleibt immer dasselbe: Freilegung und Anfrischung der Fistel von der Scheide aus, Nahtverschluss durch direkte Vereinigung der Ränder in verschiedenen, der Form und Grösse des Defektes angepassten Figuren. Geschickten und geübten Händen gelingt es in der grossen Mehrzahl der Fälle, mit dieser Methode zum Ziele zu kommen, und für alle gewöhnlichen Fälle von Blasenscheidenfistel wäre es eine überflüssige Künstelei, das einfache Verfahren durch kompliciertere zu ersetzen.

Neben der Mehrzahl günstiger Fälle giebt es aber eine Mindersahl ungünstiger, in denen dieses Verfahren mit sehr erheblichen Schwierigkeiten zu kämpfen hat und nicht selten trotz wiederholter Operationsversuche vollständig im Stiche lässt. Winckel[1]) berechnet, dass über ein Zehntel aller Frauen mit Harnfisteln ungeheilt bleibt.

Zu den ungünstigen Fällen von Harnfisteln gehören zunächst die Blasenscheidengebärmutterfisteln und die Harnleiterscheidenfisteln, sodann

1) Winckel, Die Krankheiten d. weibl. Harnröhre u. Blase. Deutsche Chir. 62. 1885. Klin. Vorträge, 355. (Chirurgie No. 109.) 255

FIG. 5. First page of Trendelenburg's paper (10) of 1890, published after 10 years' experience with the elevated pelvic position.

during inversion at a 45 degree angle. He therefore recommended never using this extreme posture for more than 5 to 10 minutes without interruption, and cautioned against using it at all for the obese or patients with congestive heart disease.

In historical perspective Trendelenburg made two principal contributions to the operative posture that bears his name: (1) popularization of the position, and (2) invention of a metal operating table fitted with padded shoulder braces and specifically designed to maintain elevation of the patient's hips and flexion of the knees.

Friedrich Trendelenburg was born in Berlin, May 24, 1844. His father, Adolf Trendelenburg, who was professor of philosophy in the University, taught him Latin and arithmetic at home, while his mother instructed him in English, his aunt in grammar. After completing his formal schooling in the Joachimsthal Gymnasium, he entered the medical school of the University of Berlin, but spent part of his time in Edinburgh and Glasgow, studying anatomy, embryology, and physics. After graduation in 1866, Trendelenburg entered military service for the next 2 years, working as surgeon in the hospitals in Gorlitz and Kiel. His thesis in ancient Indian surgery, entitled *De veterum Indorum chirurgia*, was published in 1867. From 1868 to 1874 he served as assistant to von Langenbeck, with whom he helped found the German Society of Surgeons in 1872; and in 1898 Trendelenburg was elected its chairman. In 1874, at age 30, he was made director of the surgical ward in the Friedrichshain Hospital in Berlin, and the following year was called to the University of Rostock as ordinary professor of surgery. Here he remained until 1882, when he accepted a similar position at the University of Bonn. In 1895 he responded to an invitation to the University of Leipzig, where he occupied the chair of surgery until 1911. He then retired to Nikolassee, a southwest suburb of Berlin, where he died of a malignant tumor of the lower jaw, December 15,[1] 1924, in his eighty-first year. His autobiography, *Aus heiteren Jugendtagen*, was published shortly before his death.

Entering the practice of surgery soon after the introduction of antisepsis and general anesthesia, Trendelenburg found fertile fields for his wide interests and boundless energy. He performed the first gastrotomy for stricture of the esophagus in Germany and was one of the first to ligate the hypogastric veins for puerperal pyemia. His fields of special interest included orthopedic, vascular, and plastic surgery. To the last he made noteworthy contributions on exstrophy of the bladder, harelip, and cleft palate. He also published a monograph on trigeminal neuralgia.

Trendelenburg's name is associated with an impressive list of eponymics in addition to the Trendelenburg position, for which he is best known. These include a cannula, a sign, a symptom, a test, and 4 operations. The Trendelenburg cannula, a tube fitted with an inflatable rubber collar, was designed to prevent the aspiration of blood after tracheotomy. The Trendelenburg sign, of congenital dislocation of the hip, consists of falling rather than elevation of the gluteal fold on the sound side when the patient stands on the affected leg and raises the other. Trendelenburg's symptom is the waddling gait resulting from paralysis of the gluteal muscles. The Trendelenburg test determines the competency of the venous valves in patients with varicosities of the leg. The

[1]Some of Trendelenburg's biographers have given December 16 as the date of his death.

4 operations named for Trendelenburg consist of (1) a method of excision of varicose veins, (2) ligation of the great saphenous vein to prevent reflux into varicosities, (3) surgical removal of a pulmonary embolus, and (4) the insertion of an ivory peg into the knee joint for the correction of a slipping patella. A *Festschrift* (volume 129) of the *Deutsche Zeitschrift für Chirurgie* was published in Trendelenburg's honor in 1914, on the occasion of his seventieth birthday.

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Reviews of New Books

THE MEMORIAL VOLUME of the Lyon Chirurgicale, edited by Pierre Mallet-Guy,[1] consists of 48 original articles dedicated to the memory of Professor René Leriche by his pupils from almost every corner of the world. Six Americans have had the rare privilege of studying under this outstanding teacher, clinical surgeon, and surgical philosopher of France. The unsolicited remarks as prologues to the scientific contributions attest to their love for "Le Patron" and the influence he had upon the malleable minds of all his assistants. Such ability to hold, for years and years, the deep respect, admiration, and love of their pupils is an accomplishment attained by only a few of our great teachers.

Sir James Learmonth, in his tribute to Professor Leriche in this volume repeats the now famous thumbnail sketch which he delivered when he presented "Le Patron" with an Honorary Fellowship in the Royal College of Surgeons of Edinburgh: "Indeed he is at heart a physiologist, pursuing clinical research. He is cast in the Hunterian mould: his restless mind is never satisfied—like John Hunter he is a peripatetic 'Why'. And so acute are his powers of observation and deduction, so illuminating the flashes of inspiration which he directs upon his problems, that there are few—if any—surgeons of his generation who, having asked themselves 'Why', have been able to reply 'Exactly thus' as often as has René Leriche."

Such was the spirit of this great man. Surgeons have lost a true colleague, a humble but brilliant scientist, and a great Citizen of the World.

The scientific contributions in this volume are in keeping with the high ideals and meticulous work of René Leriche. The contributions touch on most of the important fields of surgical investigation and surgical practice, and they are well written and well illustrated. This volume is a worthy tribute to the accomplishments and to the memory of an outstanding surgeon and teacher. —*Louis G. Herrmann.*

THE WELL WRITTEN BIOGRAPHICAL SKETCHES of two distinguished British surgeons[2,3] afford an interesting study in contrasts.

Sir Arbuthnot Lane and Sir John Bland-Sutton were born within a year of one another—1856 and 1855. Both attained fame and distinction in their profession, but they lived in two different worlds—the world of Guy's Hospital and the Middlesex; and as far as one could tell from these small volumes neither ever heard or knew of the other. Possibly one can gain a clue to this paradox from an incident quoted by Layton (p. 113). "Sir Harold Stiles of Edinburgh was a great admirer and friend of Lane. When I was in Edinburgh after the war, relearning some surgery, Stiles turned to his students before an operation and said: 'We are very much honoured in our visitor today. We have in our theatre a man who has been house surgeon to Sir Arbuthnot Lane.' At that time this title was a hallmark that would have given the holder of it an entree into any operating theatre in Europe, with the possible exception of London."

Arbuthnot Lane came from a long line of Ulster stock, "solicitors and doctors . . . who for seven generations named their eldest sons alternately William and Benjamin." He himself "cared for none of these things (ancestral records) . . . never went to visit the home of his ancestors, never had any interest in history or other things of the past, having set his eyes firmly all his life on the future, looking upon things of today only as stepping stones to the far tomorrow."

His medical education began at a youthful age. "I was sixteen years of age when I entered Guy's in May 1873 and looking very young was regarded as somewhat of a child by the students generally, who seemed to me to be quite old. At that time many had beards or moustaches and wore top hats. However I managed to survive" (p. 12).

Anatomy formed a very important part of the medical course. Courses of lectures and dissections were followed by an appointment as assistant demonstrator, then prosector—to prepare dissections for demonstration by the lecturer. Work as a ward clerk, assistant surgeon's clerk, dresser in surgery, assistant surgeon's dresser followed, and occupied the remainder of the first two and one-half years. Only after this period did work in the medical wards begin.

To the American reader the medical slang of "clerk," "dresser," "full surgeon's dresser," "did clinical," etc. is difficult to follow and understand; and still more difficult of comprehension is the complicated system of examinations which compelled Lane (and others) "either to go back and do all their study again or to forswear the highest attainments in the teaching world of medicine. It had not been entirely ironed out by the outbreak of the Second World War and more than one of Lane's juniors on the staff of Guy's had had to go back and do the whole curriculum again. Lane had to take this step backwards twice . . . " (p. 23) simply because the examinations which he had passed in Edinburgh were not considered an adequate test of his qualification for the fellowship of the College of Surgeons in England.

In December 1881, having passed with honors the many tests required for fellowship in the Royal College of Surgeons, he was appointed House Surgeon to the Victoria Hospital for Children and "in nine months Lane became . . . a fully-equipped operating surgeon." The reader may wonder at this statement for the writer goes on, "Lane became a surgeon through the night work of a small children's hospital over a period of nine

[1]HOMMAGE A RENÉ LERICHE. By his students. Edited by P. Mallet-Guy. 494 pages, 197 illustrations. 3.000 fr. Paris: Masson et Cie, 1956.

[2]SIR JOHN BLAND-SUTTON, 1855–1936. By W. R. Bett, M.R.C.S. (Eng.). Foreword by Lord Webb-Johnson. 100 pages, 5 illustrations. $4.75. Baltimore: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone Ltd., 1956.

[3]SIR WILLIAM ARBUTHNOT LANE, BT.; AN ENQUIRY INTO THE MIND AND INFLUENCE OF A SURGEON. By T. B. Layton, D.S.O., M.S. 128 pages, 8 illustrations. $4.75. Baltimore: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone Ltd., 1956.

months. Not that this work amounted to very much. The appendix had not then been touched, intussusception was not submitted to operation. Diphtheria was a deadly disease rampant among the poor, and he probably had many tracheotomies to perform with but a poor chance of recovery. There was, however, one subject that was coming to the fore, that of the abscess around the lung known as empyema. This gave promise of great advances in the near future with the advent of Lister's new technique and this Lane made his own for the time."

In October, 1882, Lane returned to Guy's to become demonstrator of anatomy. Whether or not he was a good teacher may be open to question. "Students used to say: 'Don't let Lane touch your part or you will have none of it left' and that when Lane sat down to a part he started rapidly dissecting. He named all the structures as they came into view, then again as he removed them, and then having done all the dissection that could be done on the part he would say: 'Dear me, I am afraid I have spoiled your part. I am so sorry' " (p. 48). But as to his energy and thoroughness there can be no question. "Night after night, as bachelor or young married man, he sat and scraped the last little bits of flesh off the bones of the bodies there, after the students had done their work on them, till the ligaments only remained. Night after night, till midnight or past, the lonely worker toiled in a great dingy room in a dingy building at the far end of the Park, away from the wards of the hospital and lit by a single gas jet which threw a gleam around the head and hands of the solitary craftsman intent upon his work, surrounded by but ignoring the corpses that lay upon the other tables, half dissected and covered by wet rags to prevent them being too dry for the students next day to continue their tasks upon them. In this way he examined the bones and ligaments of thirty-five men and women, denizens of South London, hard working with the heavy labour that fell to the lot of the very poor of those days" (p. 50). As a result of these dissections, he concluded that changes in the bones and joints resulted from the constant stresses to which they had been subjected. His conclusion: "The skeleton represents the crystallization of lines of force."

The observations that he made in the dissecting room became the basis for a philosophy by which he stood to the end of his life. At the age of 80, he prefaced a bibliography of his writings with these words, "We bear a simple mechanical relationship to our surroundings; any change in that relationship produces a corresponding alteration in our anatomy. Everything that nature does to meet such an alteration in our mechanical relationship to our surroundings tends to shorten our life."

The years in the dissecting room were marked by a veritable flood of papers from Lane's pen, many of them relatively brief, recording unusual conditions encountered in the course of his anatomic studies: Fractures of the Sternum; Costal and Sternal Asymmetry; Abnormalities Observed in the Dissecting Room During the Winter Session, 1882-83; Extensive Thrombosis Following Fracture of Both Bones of the Forearm; Ununited Fractures of Ribs; Cases of Mollities Ossium; Rheumatic Arthritis and Charcot's Disease. (These titles are taken from the "Bibliography of the Published Writings of Sir William Arbuthnot Lane—1883–1938.") Five papers in 1883, 19 in 1884, 15 in 1885, 10 in 1886, 13 in 1887—for the *Journal of Anatomy and Physiology*, the *Transactions of the Clinical Society*, the *Lancet*, the *British Medical Journal*, and more frequently for the *Transactions of the Pathological Society*, indicate how seriously and intensively he pursued his studies. After he received the coveted appointment on the surgical staff there was no letup in the contributions; only the subjects changed. Instead of reports of unusual anatomic pathologic conditions, there was a steady stream of papers describing interesting and unusual surgical cases. With increasing frequency there appeared reports on subjects that held for him special interest—middle ear infection, mastoid infection, sinus thrombosis, saline transfusion to replace loss of blood, cleft palate, and, beginning in 1893, papers on the operative treatment of fractures.

The opposition that he aroused by his advocacy of the open treatment of fractures, and later of resection of the colon are still fresh in the memory of surgeons of the present generation. One wonders how much his loneliness as a young student beginning the study of medicine at 16, as a ward clerk when "during the three months of its duration, the dressers never condescended to speak to me," how much the hours spent alone, night after night in the dissecting room may have influenced him to persist so obstinately along a certain path once he had embarked upon it. Perhaps had he been of a more gregarious nature, less of a "lone wolf," had he been willing to listen to the counsels of others, such as his friend Hale-White, he might have avoided advocating some of the radical surgical procedures with which his name has been linked, and which have now been forgotten. Unfortunately the influence of the physiologist upon surgical practice was only beginning to appear at the time of World War I. Had Lane entered upon his career 30 years later, the story might have been a different one.

From the vantage point of today, one would probably say that Lane's outstanding contribution to surgery consisted in his prompt recognition of the significance of Lister's teachings, of his introduction of Lister's methods into the surgical teaching and practice at Guy's Hospital, and, somewhat later, of the substitution of asepsis for antisepsis in surgical technique. This made it possible for him, early in his career, to become the only surgeon in London "who could open the abdomen in safety," and to carry out successfully the operative treatment of bone injuries.

He was farsighted; he often commented on the possibility of removing a lung; he visualized enlarging the stenosed mitral orifice. He lived and worked in a day when the entire field of surgery was the surgeon's province, and among the surgeons of his era he held a distinguished place.

Sir John Bland-Sutton's background was a different one. His father was "a remarkable and picturesque personality. Over six feet in height, he earned his living as a market gardener, and by fattening stock, slaughtering it, and selling it in Formosa Street, Maida Hill . . . (He) was a clever taxidermist, an authority on bird life, and an amateur medical practi-

tioner" (p. 2). Of himself Bland-Sutton said, "All my brothers but one grew up to be strong men. I remained at 5 feet 7 inches, small in bone, short in limb, weak in muscle, and always ailing and easily duped, but I learned wisdom in the stern school of experience" (p. 3).

The author continues, "Not strong enough to join in the escapades of other boys, John was left much to himself, but took a delight in watching his father dissect birds and beasts and in plying him with eager questions on their anatomical and physiological peculiarities. Then there was the thrill of visitors coming to the door with all manner of oddities such as leverets, chicks, and ducklings with two heads. When he was not roaming the countryside watching butterflies, birds, hares, frogs, and hornets in their natural surroundings, he would be immersed in some book of natural history or travel" (p. 3).

Some years later, after finishing his preliminary education, "While he was on holiday at Islington, a clumsy assistant at the Bland cattle depot stuck a knife into the middle finger of John's right hand, laying open the joint. The wound turned septic, and the patient became acutely ill. Amputation was then decided on, but at the last minute the surgeon changed his mind. The finger was saved, but the proximal interphalangeal joint remained permanently flexed at a right angle. William Henry Day, the family practitioner, thought that this was 'better than no finger, since he can hold a scalpel, although he will never make a doctor, as he is not clever or strong enough.' Despite this pessimistic and woefully false prophecy Day lent his patient a dried dissection of the forearm to while away the tedium of convalescence, and from this the boy memorized the names of the bones, muscles, blood-vessels, and nerves. His interest in human anatomy being thus aroused, and judging that his knowledge of comparative anatomy picked up from his father's dissections would prove useful, he decided to become a surgeon. Having saved every penny he could, with characteristic promptitude he put his decision into effect. He had seen an advertisement of a school of anatomy in London and lost no time in seeking out the proprietor, Thomas Cooke, F.R.C.S. In March 1878 he began, in a large shed of wood and corrugated iron in a disused churchyard off Mecklenburgh Square, to dissect the human body" (pp. 5–6).

Later during the same year, "Andrew Clark, F.R.C.S., dean of the medical school and surgeon to the hospital, was sitting in his office when a young man in his twenty-third year called to see him, expressed a wish to become a perpetual student at The Middlesex, and without more ado counted out one hundred sovereigns from a bag. The dean was amazed to see so much gold accumulated at the cost of many deprivations deposited on his desk with so little ceremony. Little did he dream that the tiny fellow who neatly wrote 'John Bland Sutton' on the hospital's roll was destined to become the most famous of her sons."

Like Lane, Bland-Sutton began his studies in the dissecting room and again, "Insatiate in his thirst for knowledge worked all day and late at night and had no time for sport and social diversions." To save the cost of the "parts" for dissection he applied for the position of prosector. He "knew Gray's Anatomy from cover to cover and was then reading Sappey's treatise on the lymphatics; (he) had no difficulty in proving his superiority over all the other competitors." "This period of his life was of absorbing interest, but also of great hardship. Money was scarce. His clothes had to last a long time; he walked wherever he could, and he contented himself with a luncheon of dry biscuits and water in the prosector's room. He had lodgings in Canonbury Square, where he worked far into the night, having found that he could do with only five hours' sleep. Both before and after qualifying he coached men in anatomy for the primary fellowship, which examination he passed in the company of some of his own pupils" (p. 11).

"Few demonstrators or lecturers have been so successful in arousing the interest and holding the attention of their class. An anatomy lesson can be dry and deadly dull, but Sutton's demonstrations of a carefully dissected 'part' popularly known as 'Sutton's entertainments,' were enlivened by witty, quizzical, and flippant comments, which stuck in the students' memories. He encouraged and enjoyed repartee, which he looked upon as useful training for the oral examinations. Like his great hero John Hunter, he taught human anatomy for capital and comparative anatomy for interest" (pp. 11–12).

In 1883, a year after he had "qualified" he was appointed senior demonstrator of anatomy and also, assistant curator of the hospital museum. His interest in comparative anatomy "took him everywhere, and he was often seen making his way from the Zoological Gardens to The Middlesex with some tit-bit for dissection. One day he caused a sensation by driving up to the hospital entrance in a 'four-wheeler' with the dead body of a huge brown bear as his fellow-passenger. If he ever learned at the zoo that a rare animal had died and that Professor William Henry Flower, Conservator of the Hunterian Museum, had requested its removal to the Royal College of Surgeons, he would follow it on its last journey and watch it being dissected" (pp. 14–15).

Although he could not afford to take the unpaid post of house surgeon when he qualified, he was elected assistant surgeon to the hospital in 1886 and lecturer on anatomy in the medical school. Since no beds were allotted to the assistant house surgeon, Bland-Sutton had to resort to somewhat devious ways to build up his practice. He operated upon patients in the outpatient department and sent them home in a cab until his colleagues began to object to the practice. During the months of August and September when the attending surgeons were on vacation he "took charge of Henry Morris's beds, and on more than one occasion his chief, returning to London, was annoyed to find all his beds filled by his junior's patients, who had recently been operated upon. This frequently meant a two to three weeks' wait before he could once again assume full charge. What brought matters to a head was Sutton's tactlessness in performing kidney operations in his chief's absence. Exceedingly jealous of his reputation as the exponent of renal surgery in England, Morris felt convinced that admission of these patients had been timed for his annual departure, though Sutton swore they had

been sent to him in the ordinary way. Despite Comyns Berkeley's repeated attempts to bring the two together, they remained long estranged. Morris was unwilling to forgive and forget what he imagined to be a deliberate slight, especially as he had befriended Sutton from his student days and had shown him many acts of kindness. For that matter Bland-Sutton, too, all his life was inclined to take small things personally and to harbour offence where none was intended" (p. 20).

In 1893, the long established Chelsea Hospital for Women was closed by the medical officer of health, Louis C. Parkes, and an investigation of the sanitary conditions of the hospital and the mortality statistics carried out. As a result, a new staff was appointed by a committee appointed by the presidents of the two royal colleges, and the post of surgeon to outpatients offered to Bland-Sutton. In 1896, he became full surgeon and with 15 beds on his service he succeeded in "making this small hospital, which had had so poor a start in life, the 'Mecca for pelvic surgeons from all over the world'." In the words of Victor Bonney, who went to Chelsea as resident officer in 1898, he "raised the status of abdomino-pelvic surgery out of the narrow rut of specialism in which it threatened to stick and created the gynaecological surgeon in place of the gynaecologist." "On Monday afternoons, when he was operating, the theatre could barely hold the visitors, who included distinguished surgeons from all parts of the globe." Again in Bonney's words, "He had a remarkable power of infusing enthusiasm into those who served under him, and all of us worked with a will to make the operations go off as perfectly as possible. It was the beginning of that 'team work' which is now an established practice in all first-class surgical centers" (p. 21).

Bland-Sutton performed his first hysterectomy for fibroids in 1890, a procedure which at first was bitterly opposed as "criminal mutilation." In 1897 when he reported on the results of 28 cases of abdominal hysterectomy for uterine myoma before the Obstetrical Society of London, one speaker stated that not 1 fibroid in 20 required removal and that he hoped the lecturer's doctrines would not be accepted by others.

Gradually the opposition faded. In 1904, Bland-Sutton was asked to open a discussion on the indications for hysterectomy before the surgical section of the British Medical Association. In the years that followed he "became the leading gynaecological surgeon of his day, and he made a fortune out of hysterectomy"—an observation that may arouse some wistful repercussions among surgical specialists of the present generation.

In 1911 he resigned his position at the Chelsea Hospital which he had done so much to make famous and which in turn "had provided him with every facility for achieving his great position." "The real reason was that he had made five unsuccessful attempts at being elected to the council of the Royal College of Surgeons of England (1900, 1901, 1902, 1904, 1909). Sir Thomas Barlow told Webb-Johnson that the reason for Bland-Sutton's repeated defeat was his connexion with a 'Woman's Hospital'. Webb-Johnson explained this to Bland-Sutton, who the following day resigned from Chelsea and refused a consulting post" (p. 29.). Early in his career he had set as his goal the presidency of the Royal College of Surgeons, and this honor he achieved in 1923, when he was elected president as successor to Sir Anthony Boweby.

Bland-Sutton's interest in comparative anatomy and in pathology was marked by many memorable contributions. His Erasmus Wilson lectures before the College of Surgeons on: "Evolution and Disease" (1886-1891); "Ligaments, their Nature and Morphology," first published in 1887; his Jacksonian essay, "On Diseases of the Ovaries and Fallopian Tubes" (1890); his "Tumours, Innocent and Malignant," first published in 1893 and subsequently reprinted and revised a number of times, brought him both fame and an international reputation.

Many interesting sidelights on his life and career—his travels to far off climes, his many friendships with men and women in every walk of life, his home with the replica of the Hall of Honour from the palace of Darius, the Great, at Susa, his generous gift to make possible the erection of the Institute of Pathology at the Middlesex—are faithfully described to help bring back to life this unusual and forceful surgeon who early in life set a goal before him, and never let anything stand in his way that might prevent him from attaining it. —*Sumner L. Koch.*

THIS VOLUME published by the American Cancer Society, Inc. entitled *Cancer of the Lung*[4] presents the essence of the discussions on the subject that took place during the Scientific Sessions of November 3 and 4, 1953, at the annual meeting. It appears in the form of a brochure, but illustrations such as photomicrographs and roentgenograms are catalogued and collected at the end of the book. They are very beautifully reproduced. At first perusal, little interest was generated because familiar references were encountered and it appeared to be merely a review of standard issues commonly debated. More careful scrutiny however, whets one's interest because it carries the reader through the various facets of the problem.

The introduction labels the disease "The most striking feature of the contemporary epidemiological scene, all diseases included." From this introduction it develops current thought on incidence, etiology, genetics, detection, diagnosis, and treatment. From the standpoint of etiology various agents are discussed including tobacco and air pollution. Likewise the possible effects of such occupational or environmental factors as chromates, arsenicals, beryllium, asbestos, and radioactive dusts are brought to light. The value of carefully read roentgenograms of the chest, particularly if comparisons with earlier films are available, is emphasized among the other approaches to diagnosis. Treatment in all modalities is portrayed. Surgical methods range from exploratory thoracotomy as a diagnostic tool to the so called radical pneumonectomy. X-ray irradiation in several forms as well as chemotherapy are accorded their place in the discussion.

[4]CANCER OF THE LUNG; AN EVALUATION OF THE PROBLEM. Proceedings of the Scientific Session, Annual Meeting, American Cancer Society, Inc., November 3–4, 1953. 322 pages, illustrated. New York: American Cancer Society, Inc., 1956.

In summary, this brochure is a very welcome source from which the opinion of high authority can be concisely taken on most, if not all of the facets of the lung cancer problem. Although synoptic in character the discussions are in the main clear and pointedly reflect the view of the presenting authority. Opposing views on controversial points tend to make for completeness. —*Hiram T. Langston*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Munro Kerr's Operative Obstetrics. Edited by J. Chassar Moir, Hon. LL.D., M.A., M.D., F.R.C.S. (Ed.), F.R.C.O.G. 6th ed. 1008 pages, illustrated. $20.00. Baltimore: The Williams & Wilkins Co., 1956.

Human Cancer; a Manual for Students and Physicians. By Maurice M. Black, M.D., and Francis D. Speer, M.D., F.C.A.P. 273 pages, illustrated. $7.50. Chicago: The Year Book Publishers, Inc., 1957.

The Principles and Methods of Physical Diagnosis; Correlation of Physical Signs with Certain Physiological and Pathological Changes in Disease. By Simon S. Leopold, M.D. 2nd ed. 537 pages, 379 illustrations and 25 colored plates. $9.00. Philadelphia and London: W. B. Saunders Co., 1957.

Gifford's Textbook of Ophthalmology. By Francis Heed Adler, M.D. 6th ed. 499 pages, 277 illustrations and 26 colored plates. $8.00. Philadelphia and London: W. B. Saunders Co., 1957.

Les ictères par rétention; diagnostic médico-chirurgical. By J. Caroli. In collaboration with A. Charbonnier, J. Étevé, A. Paraf, and P. Ricordeau. 481 pages, 308 illustrations. Paris: Masson & Cie, 1956.

Atlas of Clinical Endocrinology; including Text of Diagnosis and Treatment. By H. Lisser, A.B., M.D., and Roberto F. Escamilla, A.B., M.D. 476 pages, 148 illustrations including 3 in color. $18.75. St. Louis: The C. V. Mosby Co., 1957.

A Handbook of Operative Surgery: Surgical Gynecology; including Obstetric Operations. By J. P. Greenhill, M.D. Illustrated by Angela Bartenbach. 2nd ed. 377 pages, 107 illustrations. Chicago: The Year Book Publishers, Inc., 1957.

Calderwood's Orthopedic Nursing. Revised by Carroll B. Larson, M.D., F.A.C.S., and Marjorie Gould, R.N., B.S., M.S. 4th rev. ed. 701 pages, 307 illustrations. $5.75. St. Louis: The C. V. Mosby Co., 1957.

Therapeutic Exercise for Body Alignment and Function. By Marian Williams, Ph.D., and Catherine Worthingham, Ph.D. Exercise illustrations by Harold Black. 127 pages, illustrated. $3.50. Philadelphia and London: W. B. Saunders Co., 1957.

Treves' Student's Handbook of Surgical Operations. Revised by Sir Cecil Wakeley, BT., K.B.E., C.B., LL.D., D.Sc., M.Ch., F.R.C.S., F.R.A.C.S., F.A.C.S. 10th rev. ed. 594 pages, 272 illustrations. $7.50. New York: Paul B. Hoeber Inc., Medical Book Department of Harper & Bros., 1957.

Text-book of Orthopaedic Medicine; Treatment by Manipulation and Massage. By James Cyriax, M.D. (Cantab.), M.R.C.P.(Lond.) Vol. II. 373 pages, illustrated. $6.50. New York: Paul B. Hoeber Inc., Medical Book Department of Harper & Bros., 1957.

A Text-book of Surgical Pathology. By Charles F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.(Ed.). 7th ed. 730 pages, 322 illustrations. $14.00. Boston: Little Brown & Co., 1957.

Injuries of the Hand. By Ronald Furlong, F.R.C.S. 215 pages, 99 illustrations. $9.00. Boston: Little, Brown & Co., 1957.

Principles of Surgical Physiology. By Harry A. Davis, M.D., C.M., F.A.C.S. Foreword by Lester R. Dragstedt, M.D., F.A.C.S. 481 pages, 49 illustrations. $20.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1957.

Rypins' Medical Licensure Examinations; Topical Summaries and Questions. Edited by Walter L. Bierring, M.D., M.A.C.P., M.R.C.P., Edin.(Hon.). 8th ed. 964 pages, not illustrated. $10.00. Philadelphia and Montreal: J. B. Lippincott Co., 1957.

Practical Gynecology. By Walter J. Reich, M.D., F.A.C.S., F.I.C.S., and Mitchell J. Nechtow, M.D., F.A.C.S., F.I.C.S. 2nd ed. 648 pages, 215 illustrations and 17 colored plates. $12.50. Philadelphia and Montreal: J. B. Lippincott Co., 1957.

Hemorrhagic Diseases. By Armand J. Quick, Ph.D., M.D. 451 pages, 37 illustrations. $9.50. Philadelphia: Lea & Febiger, 1957.

Annual Review of Medicine. Edited by David A. Rytand and William Creger. Vol. VIII. 530 pages, not illustrated. $7.00. Palo Alto, California: Annual Reviews, Inc., 1957.

Martius' Gynecological Operations; with Emphasis on Topographic Anatomy. Translated and edited by Milton L. McCall, M.D., F.A.C.S., and Karl A. Bolten, M.D. 405 pages, with 450 illustrations by Käthe Droysen. $20.00. Boston and Toronto: Little, Brown & Co., 1957.

Les nouveaux syndromes hémorragiques; aspects actuels—diagnostic—traitement. By Paul Chevallier and A. Fiehrer. 128 pages, 25 illustrations. 1.500 fr. Paris: Masson et Cie, Éditeurs, 1957.

Some Milestones in the History of Hematology. By Camille Dreyfus, M.D. 87 pages, illustrated. $4.50. New York and London: Grune & Stratton, Inc., 1957.

International Congress of Gastroenterology. Fifth meeting of l'Association des Sociétés Européennes et Méditerranéennes de Gastro-Entérologie. London, July 18–21, 1956. 634 pages, illustrated. Basel and New York: S. Karger, 1957.

Phaeochromocytoma. By Wessel Van Schie. 165 pages, illustrated. Drukkerij: H. J. Smits, 1957.

Probleme de terapeutică. Academia Republicii Populare Romine; Institutul de Terapeutică. Vol. IV. 213 pages, illustrated. Burcuresti: Editura Academiei Republicii Populare Romine, 1956.

Buletin stiintific; sectia de stiinte medicale. Academia Republicii Populare Romine. Vol. VIII. 598 pages, illustrated. Burcuresti: Editura Academie Republicii Populare Romine, 1956.

Index bibliografic 23 August 1944—31 Decembrie 1955; Index bibiliographique; 23 Août 1944–31 Décembre 1955. Congresul National de Stiinte Medicale. 749 pages, not illustrated. Burcuresti: Editura Medicala, 1957.

Essentials of Clinical Proctology. By Manuel G. Spiesman, M.D., F.I.C.P., and Louis Malow, M.D., F.A.C.S. 3rd ed. 316 pages, 129 illustrations. $8.75. New York and London: Grune & Stratton, 1957.

AMERICAN COLLEGE OF SURGEONS

DANIEL C. ELKIN, Lancaster, Kentucky, *President*

WILLIAM L. ESTES, JR., Bethlehem, Pennsylvania, *President-Elect*

PRELIMINARY PLANS FOR THE 43rd CLINICAL CONGRESS CONVENTION HALL, ATLANTIC CITY, NEW JERSEY OCTOBER 14 TO 18, 1957

CONVENTION HALL in Atlantic City will be the headquarters for most of the programs to be held at the forthcoming 43rd annual Clinical Congress. Registration, principal scientific sessions, ciné clinics, color television, medical motion pictures, exhibits, and some postgraduate courses and forums will be scheduled in this famous hall.

General plans for the Congress will follow those of previous years, and the program will be detailed in this Journal as it develops, with the final program to be published in the October issue.

The Baxter Lectureship

One important innovation this year is the Baxter Lectureship, endowed by the Baxter Laboratories of Morton Grove, Illinois. This new lectureship will be concerned with parenteral fluid therapy, and the speaker will be a man of outstanding qualifications in this field. Wednesday at 2 p.m. is the scheduled time for this new lecture.

College sponsorship of a week of study for outstanding medical students, begun at the San Francisco Clinical Congress last year, proved so successful that the program is being enlarged this year to include students from 37 medical schools. Represented this year will be students from schools in Chicago, the East, Canada, and Puerto Rico. These students are selected by vote of their fellow classmates. Dr. George V. Brindley, Temple, Texas, heads this program.

Atlantic City Committee on Arrangements

Dr. Royal A. Schaaf, Newark, is Chairman of the local Advisory Committee on Arrangements for this year's Congress. Dr. Herbert D. Axilrod, Atlantic City, is Secretary. Serving under Dr. Schaaf are the following Fellows of the College:

DAVID B. ALLMAN, Atlantic City
HAROLD J. BAYER, Atlantic City
RALPH J. BELFORD, Princeton
RICHARD C. BEW, Atlantic City
SAMUEL A. COSGROVE, Jersey City
BENJAMIN DAVERSA, Spring Lake
ARTHUR DINTENFASS, Atlantic City
MORRIS GOTTLIEB, Atlantic City
ROBISON D. HARLEY, Atlantic City
STUART Z. HAWKES, Newark
V. EARL JOHNSON, Atlantic City
PHILIP J. KUNDERMAN, New Brunswick
J. HAROLD MACART, South Orange
ANDREW F. MCBRIDE, JR., Paterson
JAMES HENRY MASON, III, Atlantic City
PAUL MECRAY, JR., Camden
ANTHONY G. MERENDINO, Atlantic City
HERBERT A. SCHULTE, Newark
CHARLES H. DeT. SHIVERS, Atlantic City
JAMES H. SPENCER, Newton
EDWARD W. SPRAGUE, Newark
G. RUFFIN STAMPS, Atlantic City
HARRY SUBIN, Atlantic City

Members of the Press Relations Committee follow:

J. MONTGOMERY DEAVER, Philadelphia, *Chairman*
WILLIAM W. L. GLENN, New Haven
SAMUEL P. HARBISON, Pittsburgh

C. Everett Koop, Philadelphia
Charles L. Munson, Wilmington
Lloyd W. Stevens, Philadelphia
Kenneth W. Warren, Boston
Harold A. Zintel, New York
Thomas C. Zulick, Jr., Easton, Pennsylvania

Official Meetings

On the opening evening, Monday, Dr. Schaaf will welcome visitors to the Congress, Dr. Ravdin will introduce special guests, and the Martin Memorial Lecture will be heard.

On Wednesday evening the popular Motion Picture Symposium showing new and unusual surgical techniques will be held.

On Friday evening, Initiates will be presented for Fellowship, Honorary Fellowships conferred, and new Officers inaugurated. Dr. William L. Estes, Jr., incoming President of the College, will give the Presidential Address. Tuesday and Thursday evenings are open for special activities.

The Oration on Trauma will be given this year by Dr. Harrison L. McLaughlin, speaking on the topic "Education in Trauma," at 2 p.m. Thursday. As already stated, the Baxter Lecture is Wednesday, 2 p.m.

Television, Ciné Clinics, Motion Pictures

Smith, Kline & French Laboratories, producers of the famous closed-circuit operative telecasts, will again bring surgery as it is being performed, this year from Johns Hopkins Hospital in Baltimore. All of the operations to be televised will employ the three-way conversational hookup between the operating surgeon, a panel of distinguished specialists, and a moderator at the auditorium. In charge of this important part of the program are Drs. Henry T. Bahnson, Baltimore, and J. Garrott Allen, Chicago, Chairman of the College's Committee on Television.

The outstanding film-lectures known as Ciné Clinics, sponsored by the Surgical Products Division of American Cyanamid Company, under the chairmanship of Dr. Hilger Perry Jenkins, Chicago, and the College's Motion Picture Committee, will be another attraction during Congress week. All films are in color, and narrated by the author. Several are being produced for this Congress and represent exceptional planning on the part of the surgeon, the College, and the surgical film production group.

Medical motion pictures made by Fellows throughout the country, and approved by the College's Motion Picture Committee, will be a continuing feature of the meeting. The evening Motion Picture Symposium will again consist of short films, with the operating surgeon explaining the procedures.

General Sessions

General sessions will begin Monday morning at 10 a.m. A preliminary glimpse of the topics follows:

Monday, 10 a.m.—Panel on Treatment of Metastatic Breast Cancer; 1:30–3 p.m.—Inflammatory Lesions of the Gastrointestinal Tract; 3:30–5 p.m.—Visceral Causes of Back Pain.

Tuesday, 1:30–3 p.m.—Tumors of the Thyroid; 2–5 p.m.—Symposium on Trauma; 3:30–5 p.m.—Panel on Portal Hypertension.

Wednesday, 1:30–3 p.m.—Panel on Changing Aspects of Surgical Infections; 2–2:40 p.m.—The Baxter Lectureship; 2:45–5 p.m.—Symposium on Cancer; 3:30–5 p.m.—Panel on Gastric Ulcer.

Thursday, 1:30–3 p.m.—Panel on Benign Lesions of the Anus and Rectum; 3–3:30 p.m.—Oration on Trauma: 4–5:30 p.m.—Annual Meeting of Fellows.

Specialty Sessions

Subjects for the specialty sessions are briefly outlined here:

GYNECOLOGY AND OBSTETRICS

Monday, 1:30–3 p.m.—Panel on Cancer and Precancerous Lesions of the Vulva; 3:30–5 p.m.—Panel on Radiation Injury to Fetus or Mother During Pregnancy.

Tuesday, 1:30–3 p.m.—Panel on Surgery of the Gravid and Puerperal Uterus (Exclusive of Simple Cesarean Section); 3:30–5 p.m.—Panel on Methods of Detecting Ovulation.

Wednesday, 1:30–3 p.m.—Panel on Management of Complications of Labor Causing Fetal Distress (Exclusive of Abruptio Placentae); 3:30–5 p.m.—Panel on Problems of Stress Incontinence.

Friday, 1:30–3 p.m.—Panel on Modern Management of Face, Brow, and Transverse Presentation: 3:15–4:45 p.m.—Endometriosis.

NEUROLOGIC SURGERY

Friday, 9–10:30 a.m.—Panel on Surgical Management of Dermoids of the Central Nervous System: 10:35–12 noon.—Panel on Traumatic Intracranial Hemorrhage; 1:30–4:45 p.m.—Symposium on Neurosurgical Subjects of Interest.

ORTHOPEDIC SURGERY

FRIDAY, 1:30–3 p.m.—Panel on Amputation in the Upper Extremity; 3:15–4:45 p.m.—Ligamentous Injuries of the Knee Joint.

PLASTIC SURGERY

MONDAY, 1:30–3 p.m.—Surgical Repair of Radiation Burns; 3:30–5 p.m.—Facial Trauma from Traffic Accidents.

THORACIC SURGERY

FRIDAY, 1:30–3 p.m.—Thoracic Surgery in Pediatrics; 3:15–4:45 p.m.—Recent Developments in Cardiac Surgery.

UROLOGY

MONDAY, 1:30–3 p.m.—Panel on Diagnosis and Management of Urinary Obstruction in the Aged.
TUESDAY, 1:30–3 p.m.—Panel on Bladder Substitutes in Congenital and Acquired Conditions.
THURSDAY, 1:30–3 p.m.—Panel on Diagnosis and Management of Surgical Lesions of the Adrenals.
FRIDAY, 1:30–3 p.m.—Panel on the Abdominal Mass in Children and Adults.

Ophthalmology and Otolaryngology

In order not to conflict with annual meetings of the American Academy of Ophthalmology and Otolaryngology being held during Congress week, the American College of Surgeons Advisory Councils in these specialties have recommended that no programs in these specialties be held in this Atlantic City Congress.

Postgraduate Courses

Eight Postgraduate Courses will be given this year and, because these classes are so popular, it is strongly recommended that you register as soon as possible. Admission will be by ticket only.

With two exceptions, all classes will meet mornings Tuesday through Friday, from 8:30 to 11:30. The exceptions are the course in Gynecology and Obstetrics, meeting Monday through Thursday, 8:30 to 11:30 a.m., and that on Surgical Aspects of Pulmonary Disease, meeting afternoons from 1:30 to 3, Monday through Thursday.

A statement on what the Postgraduate Courses are, appearing in the College *Bulletin* of May-June, is repeated here for new readers:

"The intent of these courses is to provide, within four sessions, as much current information as possible upon advances in surgery. To this end, the scope of each course is limited to a field which can be covered fully within the allotted time rather than to attempt to review a large subject in a sketchy fashion. The courses are planned with care so that they proceed by co-ordinated, progressive steps from basic facts to application to patients.

"They are designed especially for the surgeon whose opportunities for contact with research and graduate teaching are limited and for serious students who intend to pursue an entire course rather than for the occasional visitor with an hour or a half day to occupy."

Topics and Chairman follow:

Preoperative and Postoperative Care. FRANCIS D. MOORE, Boston.
Gastrointestinal Disease. S. W. MOORE, New York.
Diseases of the Liver, Biliary Tract, and Pancreas. LOUIS M. ROUSSELOT, New York.
Cardiovascular Surgery. H. WILLIAM SCOTT, JR., Nashville.
Immediate Treatment of Multiple Injuries. PRESTON A. WADE, New York.
Gynecology and Obstetrics. LOUIS M. HELLMAN, Brooklyn, New York.
Fractures in Children and in the Aged. EDWIN F. CAVE, Boston.
Surgical Aspects of Pulmonary Disease. JOHN W. STRIEDER, Brookline, Massachusetts.

Fee for the course is $5.00.

Forum on Fundamental Surgical Problems

Harris B. Shumacker, Jr., Indianapolis, and the Forum Committee believe this year's reports will continue to add stature to this renowned program. The latest research and changes and advances in surgical techniques will be presented here in at least 16 sessions during the week. These sessions will also include the specialties of Gynecology and Obstetrics, Orthopedic Surgery, Plastic Surgery, Neurologic Surgery, and Urology.

Scientific and Technical Exhibits

In selecting exhibits, timeliness and scientific and educational values are the main criteria used by the Scientific Exhibition Committee, headed by Dr. George W. Stephenson, Assistant Director of the College. Visitors to this year's exhibits will see carefully planned, and altogether informative, displays showing new results of study by research teams and surgical departments from leading medical centers.

New products, tried and true products, and refinements of these will be seen in the always interesting Technical Exhibits, and busy doctors will find time spent here highly useful in garnering new ideas and remembering essential items. Mr. Thomas E. McGinnis, Assistant Business Manager for the Clinical Congress, is in charge here, and all inquiries regarding applications and space may be addressed to him at the American College of Surgeons' Chicago headquarters, 40 East Erie Street, Chicago 11, Illinois.

Advance Registration

The Clinical Congress special Invitation Brochure, containing information about hotels, Postgraduate Courses, travel, and registration forms, has been mailed to Fellows of the College, and will be mailed to non-Fellows upon request. Early registration is strongly recommended for first choice at courses and hotel and travel accommodations. Also, anyone registering in advance will find his badge awaiting him upon arrival at the Congress and will avoid waiting in line to register.

Anyone unable to register in advance may present his credentials at the Central Registration Desk at Convention Hall. Hours there will be as follows: Sunday, October 13, from 3 to 7:30 p.m.; Monday, 8 a.m. to 5:30 p.m.; Tuesday through Friday, 8 a.m. to 5 p.m.

Fellows whose dues are paid to December 31, 1956, pay no registration fee; those whose dues are not paid up to date pay $20.00. Non-Fellows pay $20.00; members of the Federal Services, $10.00. No fee (except for Postgraduate Courses) is required of Initiates, members of the Candidate group, and surgical residents. Everyone who attends a Postgraduate Course pays $5.00.

Wives Invited

The Ladies' Entertainment Committee is planning a week of unusually pleasant activities, and doctors are cordially invited to bring their wives to this meeting.